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Parasubstituted Phenylalanine Derivatives

Parasubstituted Phenylalanine Derivates

The present invention concerns new proteinase inhibitors which contain phenylalanine as their basic structure in which the aromatic group is substituted in the para position. Through variation of the substituent on the phenylalanine group, insertion of acid amino acid in the $N\alpha$ position or C-terminal introduction of in particular heterocycloaliphatic amino carboxylic acids with hydrophobic properties, inhibitors with improved bioavailability were discovered.

Proteinase inhibitors are potential pharmaceutical preparations which can be used to control physiological processes triggered and sustained by proteinases. For numerous endogenous or naturally occurring anticoagulants it has been shown that in vivo they influence proteinase activity and are able to attenuate hyperproteolytic conditions [see Hörl, W.H. in: Design of Enzyme Inhibitors as Drugs, pp. 573-581, (Sandler, M. and Smith, H.J., eds.), Oxford, New York, Tokyo: Oxford University Press, 1989]. Owing to their particular protein structure, however, the therapeutic application of these relatively high-molecular inhibitors is limited. Because, on the one hand, these inhibitors are not resorbable in the intestine following oral application and, on the other, exert an antigenic activity, a search was made for synthetic micromolecular enzyme inhibitors.

The four classes of enzymes responsible for proteinase-dependent processes comprise the serine, thiol, metallo- and aspartate proteinases. Serine proteinases are proteolytic enzymes which possess a reactive serine group in the active site. Belonging to the trypsin family of serine proteinases are enzymes which, like trypsin, split as such C-terminal peptide bonds of the basic amino acids arginine and lysine. Of particular physiological significance in this group are those enzymes which trigger coagulation and fibrinolysis in the blood, release kinine and bring about complement activation or those which are themselves components of the enzyme systems cited.

Clotting is triggered through zymogen activation via two different paths. The first, endogenous pathway, results in clotting through a blood component-induced chain reaction. The second, exogenous pathway results in coagulation via a shorter, chain reaction-based reciprocal action between blood and tissue components. Both pathways cause activation of the zymogen factor X to serine proteinase factor X_a which, in turn,

catalyses the activation of prothrombin to the fibrinogen-coagulating serine proteinase thrombin. As a common product of both the endogenous and exogenous activation process, factor X_a was initially viewed as a preferred target enzyme for inhibiting interference in the clotting process (Tidwell, R.R. et al., Thromb. Res. 19, 339-349, 1980). Most recently, however, it was demonstrated that synthetic factor X_a inhibitors are not effective in vitro and in vivo as anticoagulants (Stürzebecher, J. et al., Thromb. Res. 54, 245-252, 1989) or as antithrombotic agents (Hauptmann, J. et al., Thromb. Haemostas. 63, 220-223, 1990). For this reason, the development of anticoagulatively effective inhibitors concentrates on discovering thrombin inhibitors.

Trypsin is itself capable of triggering hyperproteolytic conditions in the pancreas, that is, in the gland in which it is formed as zymogen. One must proceed from the premise that traces of trypsinogen are activated in the gland to trypsin and that the trypsin formed also converts other proenzymes into the enzymatically active form.

The switching off of trypsin activity by inhibitors would, accordingly, be an effective action in preventing activation processes. Because inhibition must, however, take place primarily in the gland, the inhibitor must get into the cells of the pancreas. As a miniprotein, the naturally occurring inhibitor aprotinin, however, has no chance of doing so in vivo, but is able to favorably influence secondary events (shock). In contrast thereto it could be shown with micromolecular inhibitors derived from the 4-guanidino benzoic acid that in experimental pancreatitis in rats, compounds of this kind are able to reduce enzyme activity in both the gland and in the blood (Iwaki, M. et al., Japan. J. Pharmacol. 41, 155-162, 1986).

Benzamidino derivates for the development of synthetic inhibitors for trypsin and its related enzymes have been widely investigated (Stürzebecher, J. et al., Acta Biol. Med. Germ. 35, 1665-1676, 1976).

Amino acid derivates with benzamidino structure and para amidino group have proven to be good basic structures for the development of effective trypsin inhibitors. Thus, of the benzamide type, the amino acid derivate Nα-(2-naphthylsulphonyl)-glycyl-4-amidino-phenylalanine-piperidide is the strongest thrombin inhibitor heretofore described (K_i= 6 x 10^{-9} mol/liter). With a K_i of 7.9 x 10^{-7} mol/liter, the inhibitor

designated as NAPAP ranks among the effective trypsin inhibitors (Stürzebecher, J. et al., Thromb. Res. 29, 635-642, 1983).

Further inhibitor types are also known which also effectively inhibit trypsin and thrombin: a first group comprises peptidyl-arginine-chloromethyl ketones, e.g. Dns-Glu-Gly-Arg-CH_2Cl, which inhibits trypsin (Kettner, C. et al., Meth. Enzymol. 80, 826-842, 1981) and H-D-Phe-Pro-Arg-CH_2Cl, which also inhibits thrombin (Kettner, C. et al., Thromb. Res. 14, 969-973, 1979). A second group includes peptide argininal dehyde, e.g., Boc-D-Phe-Pro-Arg-H and H-D-Phe-Pro-Arg-H (Bajusz, S., Int. J. Peptide Protein Res. 12, 217-221, 1978), which inhibit trypsin and thrombin with comparable affinity. These inhibitors, however, are unstable and, owing to their great reactivity, cause undesired secondary reactions. Trypsin and thrombin are likewise inhibited in a time-dependent reaction by the boron acid derivate Boc-D-Phe-Pro-Boro-Arg-$C_{10}H_{16}$ (cf. European patent application No. 0 293 881). The selective thrombin inhibitor (2R,4R)-4-methyl-1-[Nα-(3-methyl-1,2,3,5-tetrahydro-8-quinoline-sulfonyl)-L-arginine]-2-pipecolic carboxylic acid also has a certain trypsin-inhibiting activity (Kikumoto, R. et al., Biochemistry 23, 85-90, 1984).

Described as therapeutically applicable, non-selective inhibitors which, among other things, inhibit trypsin and thrombin are methane sulphonate of the 4-(6-guanidino-hexanoyloxy)-benzoic acid ethyl ester (Muramatu, M. et al., Biotic. Biophys. Acta 268, 221-224, 1972) and dimethane sulphonate of the 6-amidino-2-naphthyl-p-guanidino benzoic acid (cf. US patent No. 4 454 338), proposed for the treatment of acute pancreatitis (Iwaki, M. et al., Japan. J. Pharmacol. 41, 155-162, 1986)..

All benzamidino derivates heretofore tested possess unfavorable pharmacodynamic and pharmacokinetic properties for a therapeutic application. They are not resorbed in the intestine when orally administered, are quickly eliminated from circulation and their toxicity is relatively high. This applies to both N-α-arylsulphonylated 4-amidino-phenylalanine amides (Markwardt, F. et al., Thromb. Res. 17, 425-431, 1980) as well as to N-α-aryl-sulphonyl-aminoacylated 4-amidino-phenylalanine amides (cf. patent application No. DD-A-235 866). The strong basic amidino function is responsible for the insufficient pharmacological properties (Kaiser, B. et al., Pharmazie 42, 119-121, 1987).

Attempts at substituting the strong basic amidino function in highly effective inhibitors with weaker basic groups were unsuccessful; such changes would have resulted in a significant loss of potency (Stürzebecher, J. et al., Pharmazie 43, 782-783, 1988). The introduction of a carboxyl group into the inhibitor to reduce basicity of the amidino function also led to a drop in inhibitor activity. Thus, 4-amidino-phenylalanine derivates possessing C-terminally an amino acid with free carboxyl group are inhibitorily completely ineffective (Wagner, G. et al., Pharmazie 39, 16-18, 1984; Vieweg, H. et al., Pharmazie 39, 82-86, 1984).

NAPAP modification through introduction of a substituent at the α-nitrogen, which resulted in a slight increase of antithrombotic activity (cf. European patent application No. FR-A-2 593 812) also brought no improvement in pharmacological properties (Cadroy, Y, et al., Thromb. Haemostas. 58, 764-767, 1987).

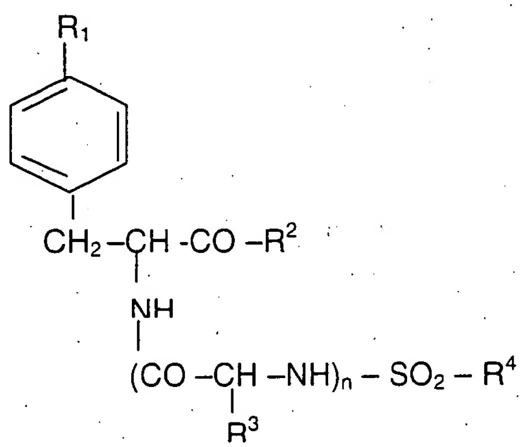
In the meantime, favorable conditions for the development of selective trypsin inhibitors do exist. Consequently, the x-ray crystal structures of trypsin complexes are known not only with benzamidino (Bode, W. and Schwager, P., J. Molec, Biol. 98, 693-717, 1975) and its simple derivates (Walter, J. and Bode, W., Hoppe-Seyler's Z. physiol. Chem. 364, 949-959, 1983), but also with the thrombin inhibitors Nα-(2-naphthylsulphonyl)-glycyl-4-amidino-phenylalanine-piperidide (Bode, W. et al., Eur. J. Biochem. 193, 175-182, 1990) and (2R,4R)-4-methyl-1-[Nα(3-methyl-1,2,3,5-tetrahydro-8-quinoline-sulfonyl)-L-arginine]-2-pipecolic carboxylic acid (Matsuzaki, T. et al., J. Biochem. 105, 949-952, 1989), which likewise form stable complexes.

Positing the differences in the bonding areas of the active site between trypsin and thrombin an attempt was made, through modification of the basic structures, to devise therapeutically applicable trypsin inhibitors with good pharmacological properties. Thus, it was to be anticipated that, for example, compounds with an acid amino acid instead of glycine in the inhibitor Nα-(2-naphthylsulphonyl)-glycyl-4-amidino-phenylalanine-piperidide are no longer bound to thrombin because thrombin possesses a glutamic acid group in position 192 (Bode, W. et al., Eur. J. Biochem. 193, 175-182, 1990). In contrast thereto, bondability to trypsin should be preserved and/or improved because an unloaded glutamine group is positioned in the trypsin at this site. In this framework, Nα-(2-

naphthylsulphonyl-aspartyl-4-amidino phenylalanine piperidide, for example, was produced. It was determined that this compound does not, as anticipated, selectively inhibit trypsin but, surprisingly, thrombin. It was further determined that this compound possesses improved pharmacokinetic properties and especially following subcutaneous administration in rats is resorbed through the intestine, remains available in effective, clotting-inhibiting concentration in the blood over a longer period of time and has very low toxicity. This also applies to compounds carrying heteroaliphatic amino acids in the C-terminal moiety.

The present invention relates to new proteinase-inhibiting D,L-, L- and D-phenylalanine derivates having the formula

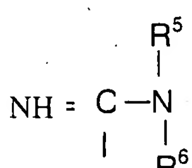
I



in which

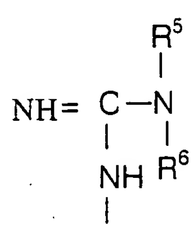
R^1 stands for a basic group of the formula

(a)



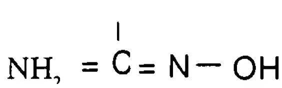
Amidino

(b)



Guanidino

(c)



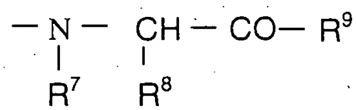
Oxamidino

(d) $-CH_2-NH_2$ Aminomethyl or (e) $-NH_2$ Amino

wherein, R^5 and R^6, in the formulas (a) and (b), designate in each case a hydrogen or a straight-chain or branched low alkyl group,

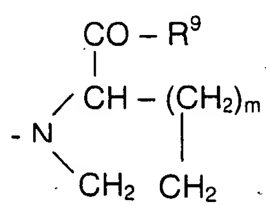
R^2 (f) can be OH, O-alkyl, O-cycloalkyl, O-aralkyl,

(g) represents a group of the formula



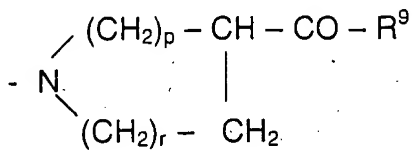
in which R^7 designates hydrogen or a straight-chained or branched low alkyl group and R^8 a straight-chained or branched low alkyl group, a 1- or 2-hydroxyethyl group, a methyl mercapto ethyl group, an aminobutyl group, a guanidino propyl group, a carboxy (low) alkyl group, a carboxamido (low) alkyl group, a phenyl (low) alkyl group, whose ring, if applicable, is substituted by OH, halogen, low alkyl or methoxy, a cyclohexyl or cyclohexyl methyl group, whose ring, if applicable, is substituted by OH, halogen, low alkyl or methoxy, or an N-heteroaryl (low) alkyl group with 3 to 8 carbon atoms in the heteroaryl, e.g., imidazolyl methyl or indolyl methyl, wherein the group (g) can be racemic or D- or L-configured,

(h) represents a group of the formula



in which m designates the number 1 or 2 and in which one of the methylene groups is possibly substituted by a hydroxyl, carboxyl, low alkyl or aralkyl group, wherein the group (h) can be racemic or D- or L-configured,

(i) represents a group of the formula



in which p = r = 1, p = 1 and r = 2 or p = 2 and r = 1 and in which one of the methylene groups is possibly substituted by a hydroxyl, carboxyl, low alkyl or aralkyl group,

(k) represents a piperidyl group which is possibly substituted in one of the positions 2, 3 and 4 by low alkyl, hydroxyalkyl or hydroxy group,

wherein a further aromatic or cycloaliphatic ring, preferably phenyl or cyclohexl, can be fused to the heterocycloaliphatic rings of the formulas (h), (i), (k) in the 2,3 or 3,4 position, referenced to the heteroatom,

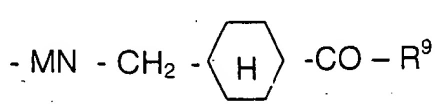
(l) a piperazyl group, which is possibly substituted in p-position by an alkyl group, a aryl group or an alkoxy carbonyl group,

(m) represents a group of the formula

$$-\underset{\displaystyle R^{10}}{\underset{|}{N}}-(CH_2)_{n'}-CO-R^9$$

in which n' designates the numbers 1 through 6 and R^{10} hydrogen or the methyl or cyclohexyl group and R^1 can be = (b) to (e),

(n) represents a group of the formula



wherein R^9 designates in the formulas (g), (h), (i), (l), (m) and (n) a hydroxyl, straight-chained or branched low alkoxy, cycloalkoxy or an aralkoxy group,

or

(o) represents a combination from 2 to 20, preferably 2 to 5, in particular 2 or 3, of the derived groups defined under (g), (h), (i), (k), (l), (m) and (n), linked together by amide bonds (R^9 = single bond), wherein the C-terminal group is possibly coupled to a group R^9,

R^3 represents hydrogen or straight-chained or branched low alkyl, aralkyl, carboxyalkyl, alkoxy carbonyl-alkyl-, carboxamido-alkyl-, heteroarylalkyl- or a 1- or 2-hydroxyethyl group, wherein n designates the number 0 or 1 and the amino acid possibly inserted can be racemic or D- or L-configured, and

R^4 represents an aryl group, e.g. phenyl, methyl phenyl, α- or β-naphthyl or 5-dimethylamino)-naphthyl, or a heteroaryl group, e.g. quinolyl,

wherein low means 1-4 carbon atoms,

and their salts with mineral acids or organic acids.

The compounds of the general formula I with R^1 = amidino (a) can be produced according to the following described, inherently known methods.

Of the phenylalanine derivates defined in the general claims, compounds in which

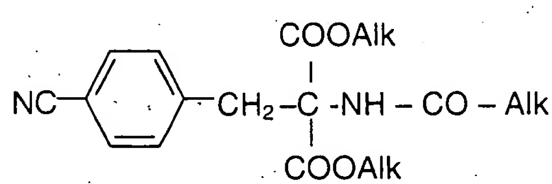
R^2 represents O-alkyl, O-cycloalkyl or aralkyl if n=0, represents a heterocycloaliphatic group explained in greater detail in the formulas (h), (i), (k) and (l),

R^4 designates β-naphthyl and

n means the number 1,

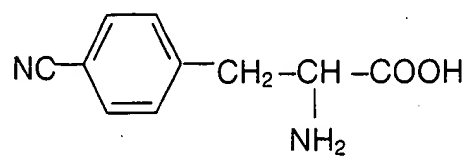
are of particular significance.

4-cyanobenzyl-acylamino-malonic acid diesters of the general formula II,

II 

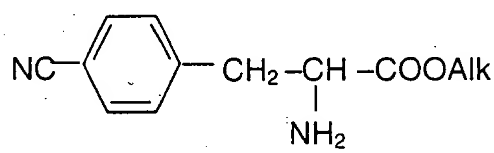
in which Alk preferably means - CH_3 or - C_2H_5, are converted in a mixture of 3 N HCl and glacial acetic acid through refluxing to 4-cyano-phenylalanine III

III



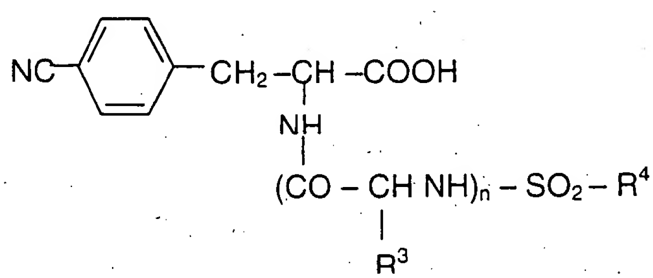
whose esterification with a low alcohol, preferably methanol, in the presence of toluene-p-sulphonic acid or sulfuric acid, results in 4-cyano-phenylalanine alkyl ester IV.

IV



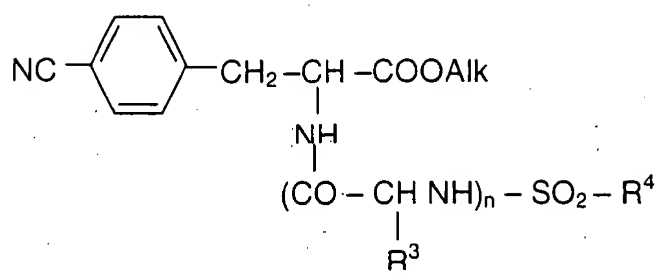
Through sulphonylation of compounds III with an aryl or heteroaryl sulphonyl chloride or acylation with a sulphonylated amino acid halogenide in the presence of a base, the compounds of the general formula V,

V



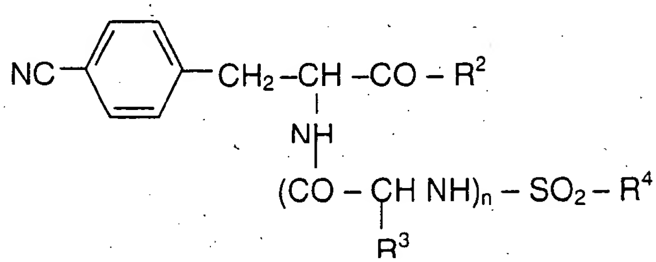
in which n = 0 or is 1 and R^3 and R^4 possess the meanings described in the general formula I, are obtained.

According to a second variant, for preparation of the compounds V sulphonylated amino acids are initially converted with the carboxylic acid ester IV in accordance with the DDC process to compounds of the general formula VI

VI 

with carboxylic acid ester structure, from which, following alkaline hydrolysis, the compounds V are obtained. The meanings of n, R^3 and R^4 in the general formula VI correspond to those of compounds V.

The compounds of the general formula VII,

VII 

in which R^2 possesses the meanings cited in the general formula I under (g), (h), (i), (k), (l), (m), (n) and (o) and R^3 and R^4 possess the meanings stated in this formula and R^9 represents a straight-chained or branched alkoxy or benzyloxy group, are prepared in accordance with a first method variant through conversion of compounds V with a corresponding amino acid ester in accordance with the mixed anhydride process by bringing structure V compounds to reaction, preferably with chloroformic acid butyl ester, in the presence of a suitable tertiary base, e.g., 4-methyl morpholine, at -15° to -20°C in an aprotic diluent and subsequently converting them with an amino acid ester or amine.

In accordance with a second method variant, the compounds of the general formula V are converted according to the DCC process with corresponding amino acid esters by bringing the compounds V to reaction in a suitable aprotic diluent with dicyclohexyl

carbodiimide in the presence of 1-hydroxybenzotriazole and converted to VII with the amino acid esters or amines cited.

In accordance with a third method variant, after conversion to active esters with, for example, N-hydroxy succinimide, 2,3,4,5,6,-pentafluorophenol or p-nitrophenol in the presence of dicyclohexyl carbodiimide, structure V compounds are isolated or converted with corresponding amino acid esters or amines to compounds of the general formula VII without interim isolation.

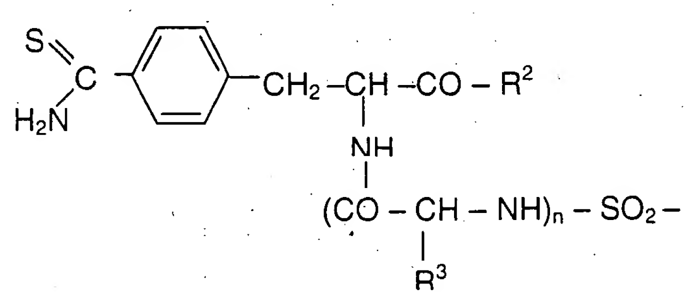
In accordance with a fourth method variant, structure V compounds, in which n = 0, are converted, for example, with thionyl chloride to acid chlorides which are subsequently converted with corresponding amino acid esters or amines to compounds of the general formula VII.

Through mild alkaline or acid hydrolysis with, for example, diluted NaOH or trifluoroacetic acid structure VII compounds, the compounds with carboxylic acid structure of the general formula VII are obtained, wherein R^2, R^3 and R^4 possess the meanings cited in the general formula I and the R^9 defined in R^2 = OH.

Proceeding from the compounds with carboxylic acid structure VII, further amino acid esters can be coupled in accordance with the processes precedingly described.

Through addition of H_2S to VII with carboxylic acid or carboxylic acid ester structure to pyridine in the presence of triethyl amine, the thioamides of the general formula VIII

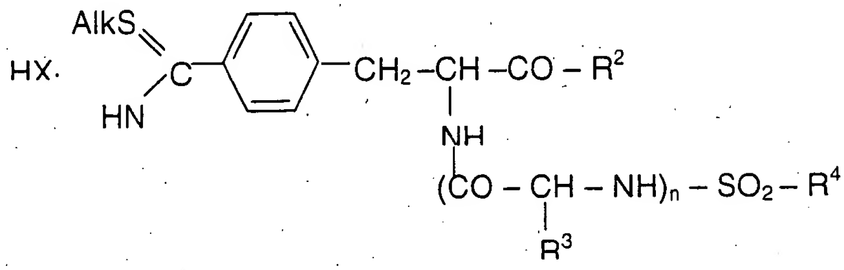
VIII



are obtained, wherein the meanings of the substituents R^2, R^3 and R^4 correspond to those of the general formula I.

Through conversion of the compounds VIII with an alkyl halogenide, preferably, methyl iodide, the thioimide acid ester halogenides IX

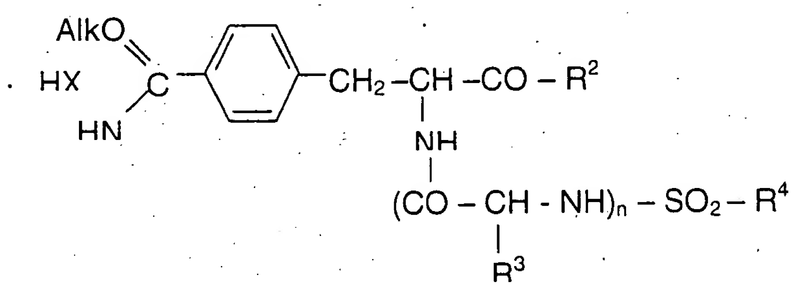
IX



are obtained. The meanings of n and R^2 through R^4 correspond to those of the general formula I, Alk represents low alkyl, preferably $-CH_3$, and X means halogen, generally iodine.

Additionally, the compounds VII can be converted with a low alcohol, possibly in the presence of a solvent like, for example, dioxane or chloroform, in the presence of anhydrous halogen hydrogen, to imide acid ester halogenides X

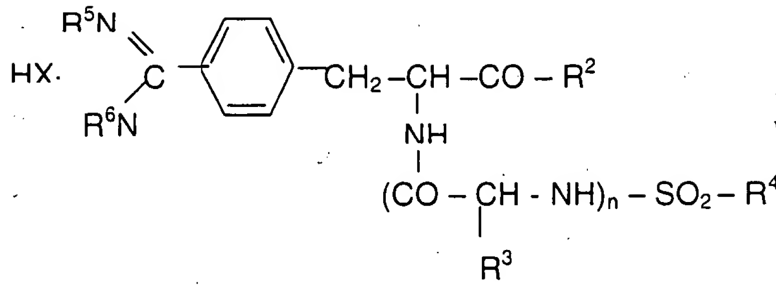
X



wherein compounds with free -COOH group are esterified at the same time with the alcohol used. The meanings of n and R^2 through R^4 correspond to those of the general formula I, Alk represents low alkyl, preferably $-CH_3$ or C_2H_5, and X means halogen, generally chorine.

To prepare the target compounds XI

XI



with n = 0 or 1 and the meanings of the substituents R^1 through R^6 analogous to those of the general formula I and X = halogen, the thioimide acid ester salts IX are converted in an alcoholic solution with ammonium acetate or an alkyl ammonium acetate or the imide acid ester salts X converted in alcoholic ammonia solution to XI.

Compounds XI with one t-butoxy group (R^9) in the substituent R^2 can subsequently be converted through hydrolysis with trifluoroacetic acid to compounds XI with carboxylic acid structure (R^9 = OH).

Compounds XI with an OH group (R^2 or R^9) can subsequently be converted, with preferably low aliphatic (C_1-C_8), cycloaliphatic or araliphatic alcohols, in the presence of hydrochloric acid or p-toluol sulphonic acid, to compounds XI with carboxylic acid structure (R^2, R^9 = O-alkyl, O-cycloalkyl, O-aralkyl).

The compounds of the general formula I with R^1 = oxamidino (c) are prepared, via the intermediate products of the formulas II through IX, on the same synthetic pathway as the compounds with R^1 = amidino (a). In the last step of synthesis, the thioimide acid ester salts IX are converted with hydroxyl ammonium acetate to compounds of the general formula I, wherein R^1 represents the oxamidino group (c).

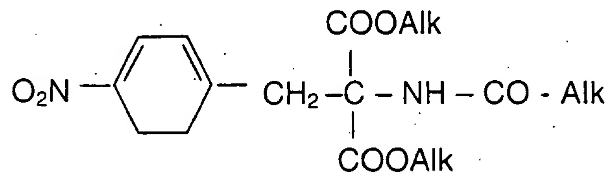
The compounds of the general formula I with R^1 = aminomethyl (d) are likewise prepared, via the intermediate products of the formulas II through VII, in the same manner. In order to arrive at the target compounds of the general formula I with R^1 = -CH_2 - NH_2, the cyano compounds VII are catalytically reduced, for example with Raney nickel hydrogen in alcoholic solution in the presence of ammonia, to the aminomethyl

compounds. The free bases obtained are converted in suitable manner to salts, preferably hydrochlorides.

The compounds of the general formula I with R[1] = guanidino (b) can in principle be prepared in accordance with the same synthetic scheme as those with amidino structure (a).

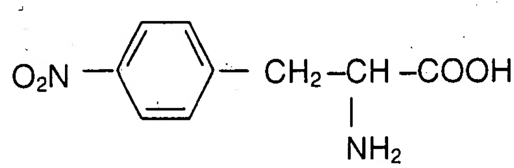
To this end, 4-nitrobenzyl acylamino malonic acid diesters of the general formula XII

XII



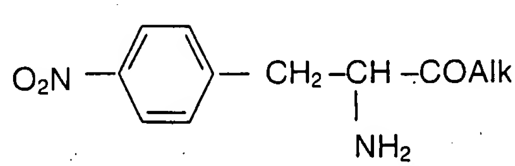
in which Alk preferably means - CH_3 or - C_2H_5, are converted through refluxing in a mixture of 3 N HCl and glacial acetic acid to 4-nitrophenylalanine XIII,

XIII



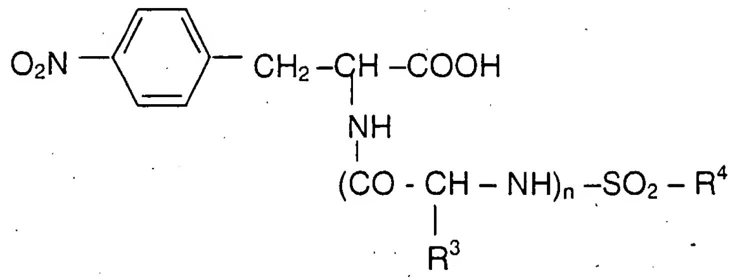
whose esterification, with a low alcohol, preferably methanol, in the presence of toluene-p-sulphonic acid, hydrogen chloride or sulfuric acid, results in 4-nitrophenylalanine alkyl ester XIV.

XIV

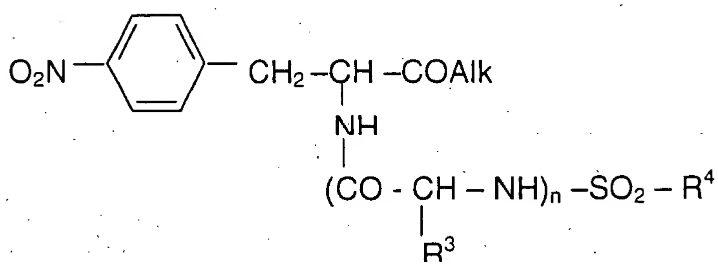


The compounds XV, XVI and XVII

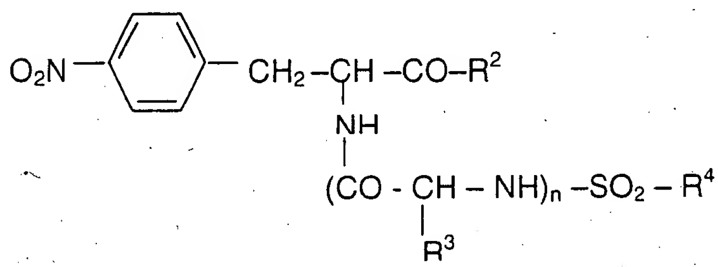
XV



XVI



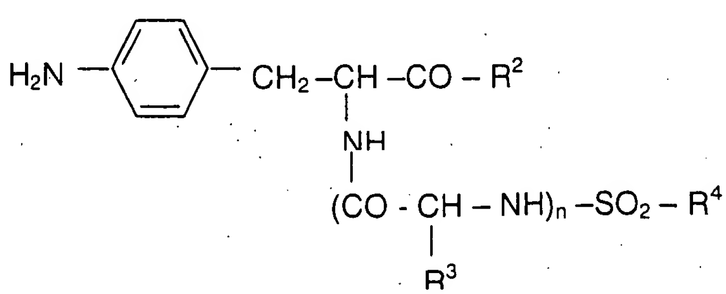
XVII



are obtained in the same manner as the corresponding cyano compounds V through VII, wherein the meanings of n, R^2, R^3 and R^4 are also corresponding.

Through catalytic hydration by means of, for example, Raney nickel hydrogen in a suitable solvent, the amino compounds of the general formula XVIII

XVIII



are obtained from XVII, which, by means of a suitable guanylation reagent, for example 1-amidino-3,5-dimethyl-pyrazole-nitrate, are converted to the guanidino compounds of the general formula I with R^1 = guanadino (b).

Compounds with the general formula I with R^1 = guanidino (b), oxamidino (c), aminomethyl (d) or amino (e) and one t-butoxy group (R^9) in the substituent R^2 can be converted through hydrolysis with trifluoroacetic acid to compounds with carboxylic acid structure (R^9 - OH), which through esterification with low alcohols, preferably methanol, in the presence of hydrochloric acid or toluene-p-sulphonic acid, can be subsequently converted to compounds with carboxylic acid ester structure (R^9 = alkoxy).

The biological activity of the compounds in accordance with the invention was determined in vitro as well as in vivo. For characterization of the inhibitor activity in vitro, the dissociation constants K_i for were measured for the inhibition of trypsin and/or the related enzymes thrombin, plasmin, factor X_a, tPA, glandular kallikrein, factor XII_a and plasma kallikrein in accordance with the formula

$$K_i = \frac{[E] \cdot [I]}{[EI]}$$

in which [E] designates the concentration of free enzyme, [I] the concentration of free inhibitor and [EI] the concentration of enzyme-inhibitor complex. (Dixon, Biochem. Vol. 55, 170-173, 1953). The smaller the K_i value for an enzyme tested is, the greater the affinity of the inhibitor for the enzyme and the smaller the amount needed of inhibitor for inhibition of the enzyme, for example, thrombin.

In vitro, different coagulation tests were used to determine the effectiveness of the inhibitors vis-à-vis the thrombin-triggered coagulation of its natural substrate, fibrinogen. To this end, thrombin time (TT), activated partial thromboplastin time (aPTT) and prothrombin time (PT, quick value) were determined in human plasma.

Toxicity of the compounds in accordance with the invention was established through determination of the LD_{50} (= dosage resulting in mortality of 50% of the experimental animals over an observation period lasting one week) in mice following intravenous and/or peroral administration.

For pharmacokinetic characterization, the plasma concentration of selected derivates after subcutaneous (s.c.) and peroral (p.o.) application in rats was determined in accordance with the following three-step process:

1. A solution of the substance to be tested in physiological saline solution was subjected to high pressure liquid chromatography (HPLC) in order to determine the characteristic peak for the substance to be tested at the substance-specific retention time under the testing conditions selected.

2. The substance to be tested was dissolved <u>in vitro</u> in rat plasma. This solution also underwent HPLC in order to determine whether the substance-characteristic peak would again appear at the substance-specific retention time.

3. The substance to be tested was dissolved in physiological saline solution and administered s.c. and p.o. to rats in a dosage of 5 and 100 mg per kg of body weight. Blood samples were taken at 15 minute time intervals, from which, through centrifuging, plasma samples were produced which, in turn, were subjected to HPLC in order to determine whether the substance-characteristic peak would again appear at the substance-specific retention time.

COMPOSITIONAL LEGEND

SS - solvent system (see below)

R_f - retention factor, with indication of 2 R_f- values, double-spot formation through isomerism

To implement the thin-film chromatographic tests, MERCK thin-film ready-to-use plates with silica gel 60, F254, as coating, and the following solvent systems (SS) were used:

SS 1: organic phase of ethyl acetate/acetic acid/water (4/1/2)

SS 2: chloroform/methanol/acetic acid (40/4/1)

Spray reagents: ninhydrin - for primary and secondary aliphatic amino groups

4-dimethylamino benzaldehyde - for primary aromatic amino groups

To implement column chromatography for purposes of raw product cleaning, silica gel 60 with a particle size of 0.035 - 0.070 mm was used.

ABBREVIATIONS in Examples 1 - 11

TEA - triethylamine

HOBT - 1-hydroxy benzotriazol

DCC - dicyclohexyl carbodiimide

NMM - 4-methyl morpholine

DMF - dimethyl foramide

THF - tertrahydrofuran

TFA - trifluoroacetic acid

HOSu -N-hydroxy succinimide

tf - thin-film chromatographic

Example 1

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanine-(D,L)-pipecolic acid (8)

(4-cyanobenzyl)-acetamino-malonic acid-diethylester (1)

10.0 g 4-cyanobenzyl bromide and 11.0 g acetamino-malonic acid-diethylester were dissolved in 100 ml abs. dioxane and, while stirring, a sodium methylate solution (1.15 g sodium/50 ml. abs. ethanol) added dropwise. The preparation was refluxed 5 hours, precipitated NaBr subsequently filtered off in the vacuum and the filtrate evaporated to low bulk in a vacuum to incipient crystallization. 250 ml water were added, the precipitate suctioned off, washed with water and recrystallized. Yield: 81%, melting point 166-168°C.

4-cyano-(D,L)--phenylalanine-hydrochloride (2)

12.0 g of compound 1 were refluxed 6 hours in a mixture of 32 ml glacial acetic acid and 64 ml 3 N HCl. The solvent was subsequently distilled off and the residue dried. The raw product obtained was dissolved in methanol and chromatographically cleaned via a column (Sephadex® LH-20, Pharmacia) with methanol as eluting agent. Yield: 70%, melting point 226-228°C.

N-α-(2-naphthylsulphonyl)-4-cyano-(D,L)-phenylalanine (3)

11.5 g of the compound were dissolved in 160 ml 1 N KOH, a solution of 12.5 g 2-naththylsulphonyl chloride added to 100 ml ether and the mixture stirred 16 hours at room temperature, whereby after approximately 1.5 hours the potassium salt of compound 3 began to crystallize out. The precipitate was subsequently suctioned off, washed with ether, dissolved under heating in water and acidified with 3 N HCl, whereby compound 3 crystallized out. It was suctioned off, washed with water and dried. Yield: 60%, melting point 184-186°C.

N-α-(2-naphthylsulphonyl)-4-cyano-(D,L)-phenylalanyl-(D,L)-pipecolic acid-ethyl ester (4)

1.35 g (D,L) pipecolic acid-ethyl ester and 0.8 g NMM were dissolved in 20 ml ethyl acetate, a solution of 3.0 g of the acid chloride obtained from compound 3 and thionyl chloride added dropwise to 30 ml ethyl acetate and the preparation stirred 2 hours at room temperature. The solvent was subsequently distilled off, the residue dissolved in 20 ml methanol and allowed to stand in order to crystallize. The precipitate formed was suctioned off and recrystallized from methanol/water. Yield: 65%, melting point 164-166°C.

N-α-(2-naphthylsulphonyl)-4-cyano-(D,L)-phenylalanyl-(D,L)-pipecolic acid (5)

2.0 g of compound 4 were suspended in a mixture of, in each case, 20 ml methanol and 1 N NaOH and the preparation stirred at room temperature until complete saponification (tf control). Subsequently,, half of the solvent was distilled off in a vacuum and the remaining solution acidified with 1 N HCl. The precipitated out, amorphous product was suctioned off, washed with water and dried. Yield: 90%.

N-α-(2-naphthylsulphonyl)-4-thiocarboxamido-(D,L)-phenylalanyl-(D,L)-pipecolic acid (6)

1.0 g of compound 5 was dissolved in 15 ml pyridine and 1 ml TEA, H_2S introduced 10 minutes into the solution and the preparation stored 48 hours at room temperature. The solvent was subsequently distilled off, absorbed in ethyl acetate and extracted out with 1 N HCl. The organic phase was washed 1 time with water, dried via $MgSO_4$ and the solvent distilled off. The isolated yellow, amorphous product was further processed in the form obtained. Yield: 85%.

N-α-(2-naphthylsulphonyl)-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-hydroiodide (7)

1.0 g of compound 6 was dissolved in 20 ml acetone, the solution mixed with 3.0 g methyl iodide and the preparation stored, protected from light, at room temperature for 20

hours, whereby compound 7 began to crystallize out. It was left another to stand 24 hours in the refrigerator, the precipitate suctioned off, washed with acetone/ether 1:1 and dried. Yield: 67%, melting point 203-205°C (decomp.)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-(D,L)-pipecolic acid-hydroiodide (8)

0.6 g of compound 7 were dissolved in 10 ml methanol, the solution mixed with 0.1 g ammonia acetate and the preparation heated gently 3 hours at 60°C in a water bath. The solvent was subsequently distilled off, the residue dissolved in ethanol and compound 8 precipitated out with ether. The precipitate formed was suctioned off, washed with ether and dried. Yield: 78%, melting point starting at 185°C.

Example 2

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-(D,L)-sarcosine and -methyl ester (15, 16)

N-α-(2-naphthylsulphonyl)-glycine (9)

A solution of 45 g 2-naphthylsulphonyl chloride in 200 ml ether was added to a solution of 16.5 g glycine in 440 ml 1 N NaOH and the reaction mixture intensively stirred 4 hours at room temperature. The aqueous phase was subsequently acidified with 3 N HCl, the precipitate suctioned off, washed with water and dried. Yield: 76%, melting point 153-154°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanine (10)

10 g of compound 2 were dissolved in 135 ml 1 N NaOH, a solution of 11.0 g of the (2-naphthylsulphonyl)-glycyl chloride obtained from compound 9 and thionyl chloride added to 120 ml ethyl acetate and the preparation intensively stirred 3 hours. Subsequently, a small amount of insoluble side product filtered off, the aqueous phase acidified with 3 N HCl and extracted with ethyl acetate. The organic phase was washed 1 time with water, dried via $MgSO_4$ and the solvent distilled off to the greatest extent

possible. The remaining residue crystallized when ground with ether. 50 ml ether were added, the precipitate suctioned off, washed with ether and dried. Yield: 68%, melting point 156-158°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl-sarcosine-t-butyl ester (11)

0.61 g sacrosine-t-butyl ester hydrochloride were dissolved in 4 ml DMF, the solution mixed with 0.74 ml NMM and a solution of 1.6 g of the N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl OSu ester obtained from compound 10, HOSu and DCC in 20 ml THF, and the reaction mixture stirred 16 hours. The solvent was subsequently distilled off, the residue absorbed in ethyl acetate, the solution washed with a 10% citric acid, saturated $NaHCo_3$ solution, dried via $MgSO_4$ and the raw product obtained after distilling off of the solvent was cleaned by column chromatography via silica gel 60 (chloroform/methanol 95:5 as eluting agent). Yield: 55%, melting point 134-136°C (from ethyl acetate).

N-α-(2-naphthylsulphonyl)-glycyl-4-thiocarboxamido-(D,L)-phenylalanyl-sarcosine-t-butyl ester (12)

1.0 g of compound 11 was converted analogous to 6 and worked up. Yield: 89%, amorphous product.

N-α-(2-naphthylsulphonyl)-glycyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-sarcosine-t-butyl ester-hydroiodide (13)

0.85 g of the thioamide 12 were dissolved in 15 ml acetone, 1.5 g methyl iodide added and the solution stored, protected from light, at room temperature for 16 hours, whereby compound 13 crystallized out. The precipitate was suctioned off, washed with acetone/ether 1:1 and dried. Yield: 94%, melting point starting at 136°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-sarcosine-t-butyl ester-hydroiodide (14)

0.85 g of compound 13 were dissolved in 15 ml methanol, 0.16 g ammonium acetate added and converted analogous to 8 and worked up. Yield: 88%, amorphous powder.

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-sarcosine-hydrochloride (15)

0.62 g of compound 14 were dissolved in 3 ml TFA and stirred 90 minutes at room temperature. Subsequently, the solvent was distilled off, the oily residue dissolved in 10 ml methanol and the solution brought to pH 7.4 with ethanolic ammonia solution. After 12 hours refrigerator storage the crystallized betain from 15 was suctioned off, washed with methanol and dried.

For conversion to hydrochloride, the betain was suspended in 5 ml methanol, the suspension acidified with a few drops of 2 N ethyl acetate/HCl and compound 15 precipitated out of the solution obtained with ether. The precipitate formed was suctioned off, washed with ether and dried. Yield: 64%, melting point 170°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-sarcosine-methyl ester-hydrochloride (16)

0.2 g of compound 15 were dissolved in 4 ml abs. methanol, 30 drops 2 N ethyl acetate/HCl added to the solution and the preparation allowed to stand 20 hours at room temperature. Through addition of ether, compound 16 was precipitated out of the reaction solution, suctioned off, washed with ether and dried. Yield: 89%, melting point 120°C.

Example 3

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-(D,L)-pipecolic acid (21)

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl-(D,L)-pipecolic acid-ethyl ester (17)

1.5 g (D,L)-pipecolic acid-ethyl ester were dissolved in 10 ml THF, 1.4 g HOBT added and the preparation cooled down to 0°C. After addition of a solution of 3.0 g of compound 10 to 25 ml THF and 1.71 g DCC it was stirred over night. The precipitated urea derivate was subsequently filtered off and the solvent distilled off. The residue was absorbed in ethyl acetate, the solution washed with water, 10% citric acid, saturated

$NaHCo_3$ solution and dried via $MgSO_4$. After distilling off of the solvent, the raw product was cleaned by column chromatography via silica gel 60 (chloroform as eluting agent). Yield: 63%, amorphous product.

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl-(D,L)-pipecolic acid (18)

2.4 g of compound 17 were dissolved in a mixture of, in each case, 25 ml 1 N NaOH and methanol and stirred in at room temperature until complete saponification (tf control). Approximately 30 ml solution were subsequently distilled off, the remaining solution acidified with 3N HCl, 100 ml water added and the precipitate formed suctioned off after standing several hours in the refrigerator, washed with water and dried. The raw product obtained was cleaned by column chromatography via silica gel 60 (chloroform/methanol 90:10 as eluting agent. Yield: 77%, amorphous product.

N-α-(2-naphthylsulphonyl)-glycyl-4-thiocarboxamido-(D,L)-phenylalanyl-(D,L)-pipecolic acid (19)

1.7 g of compound 18 were converted analogous to 6 to 20 ml pyridine and 1.5 ml TEA and worked up. Yield: 94%, amorphous product.

N-α-(2-naphthylsulphonyl)-glycyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-hydroiodide (20)

1.7 g of compound 19 were dissolved in 40 ml acetone, 6.0 g methyl iodide added and the solution allowed to stand 16 hours at room temperature protected from light. 50 ml ether were subsequently added, whereby compound 20 initially resulted in an oily product. After draining off the supernatant solvent and homogenization with ether, a solid, amorphous product was able to be obtained. Yield: 76%.

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-(D,L)-pipecolic acid-hydroiodide (21)

1.6 g of the thioimide acid ester hydroiodide 20 were dissolved in 15 ml methanol, the solution mixed with 0.28 g ammonium acetate and the preparation heated gently 3 hours at 60°C in a water bath. The solvent was subsequently distilled off, the residue dissolved

in 30 ml methanol and compound 21 precipitated out with ethyl acetate. The precipitate was suctioned off, washed with ethyl acetate and ether and dried. Yield: 75%, melting point 197-201°C.

Example 4

N-α-(2-naphthylsulphonyl)-glycyl-4-amidino-(D,L)-phenylalanyl-isonipecotine acid and methyl ester (26, 27)

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl-isonipecotine acid and ethyl ester (26, 27)

3.0 g of compound 10 were dissolved in 30 ml THF and the solution mixed with 0.7 g NMM, whereby the NMM salt from compound 10 precipitated out. After addition of 30 ml DMF the solution was cooled down, with stirring, to -4°C, 0.98 g chloroformic acid added to the suspension and stirred 30 minutes at -4°C. Thereafter, a solution of 1.62 g isonipecotine acid-ethyl ester was added to 20 ml THF, stirred another 60 minutes at -4°C and this continued at room temperature over night. The solvent was subsequently distilled off and the residue ground with methanol, whereby crystallization occurred. 50 ml 50% methanol were added, suctioned off and recrystallized from methanol/water. Yield: 68%, melting point 169-171°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-cyano-(D,L)-phenylalanyl-isonipecotine acid (23)

2.5 g of compound 22 were dissolved in a solution of, in each case, 25 ml N NaOL and methanol and stirred 1 hour at room temperature. Subsequently,, half of the solvent was distilled off, the remaining solution acidified with 1 N HCl and 150 ml water added. After standing for several hours, the precipitate formed was suctioned off, washed with water and dried. Yield: 92%, melting point starting at 110°C.

N-α-(2-naphthylsulphonyl)-glycyl-4-thiocarboxamido-(D,L)-phenylalanyl-isonipecotine acid (24)

2.1 g of compound 23 were dissolved in 20 ml pyridine and 2 ml TEA and converted analogous to 6 and worked up. The solid product obtained was suspended in 20 ml methanol, washed with methanol and dried. Yield: 70%, melting point 234-237°C.

N-α-(2-naphthylsulphonyl)-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D,L)-isonipecotine acid-hydroiodide (25)

1.2 g of compound 24 were dissolved under slight warming in 2 ml DMF, 50 ml acetone added to the solution and filtered. The filtrate was mixed with 4.0 g methyl iodide and the reaction mixture stirred 3 hours at room temperature. The mixture was subsequently poured into 250 ml ether, the precipitate formed suctioned off, washed with ether and dried. Yield: 74%, amorphous powder.

N-α-(2-naphthylsulphonyl)-glycl-4-amidino-(D,L)-phenylalanyl-(D,L)-isonipecotine acid-hydrochloride (26)

0.8 g of thioimide acid ester hydroiodide compound 25 were dissolved in 15 ml methanol, the solution mixed with 0.15 g ammonium acetate and the preparation heated gently 3 hours at 60°C in a water bath, whereby the betain of 26 crystallized out. After standing for several hours, the precipitate formed was suctioned off, washed with water and dried. Yield: 80%, melting point 235-242°C.

The conversion to hydrochloride took place in the manner described under 15. Yield: 91%, melting point starting at 165°C.

N-α-(2-naphthylsulphonyl)-glycl-4-amidino-(D,L)-phenylalanyl-(D,L)-isonipecotine acid-methyl ester hydrochloride (27)

0.2 g of compound 26 were dissolved in 5 ml abs. methanol, 50 drops 2 N ethyl acetate/HCl added to the solution and the preparation allowed to stand 20 hours at room temperature. Compound 27 was subsequently precipitated out with ether, suctioned off, washed with ether and dried. Yield: 85%, melting point starting at 145°C.

Example 5

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-, -(D,L)-aspartyl and β-methoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-piperide (35-37)

4-cyano-(D,L)-phenylalanine-methyl ester-hydrochloride (28)

20 g of compound 2 were dissolved in 150 ml abs. methanol, the solution mixed under ice cooling with 15 g concentrated H_2SO_4 and refluxed 24 hours. Subsequently,, the methanol was distilled out in the vacuum, the residue alkalized with 3 N NaOH and extracted with 500 ml ethyl acetate. The organic phase was washed 2 times with saturated NaCl solution, dried via $MgSO_4$ and the solvent distilled off. The oily residue was dissolved in 20 ml methanol and the solution acidified with methanolic hydrochloric acid, whereby compound 28 already began to crystallize out. After addition of 400 ml ether the precipitate was suctioned off, washed with ether and dried. Yield: 78%, melting point 190-192°CC.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-asparagine acid (29)

1.0 g (D,L)-asparagine acid-β-t-butylester was dissolved in 35 ml 0.33 M Na_2CO_3 solution, a solution of 1.42g 2-naphthylsulphonyl chloride added to 15 ml ether and the reaction mixture stirred 16 hours at room temperature, whereby the sodium salt of compound 29 precipitated out. 100 ml water were subsequently added and the precipitate dissolved under light heating. The solution obtained was extracted 2 times, in each case, with 50 ml ether, the aqueous phase acidified with 1 N HCl and allowed to stand for crystallization. The precipitate formed was suctioned off, washed with water and dried. Yield: 66%, melting point 138-140°C.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-cyano-(D,L) phenylalanine-methyl ester (30)

2.77 g of compound 28 were dissolved in 15 ml DMF, 1.28 ml NMM, 1.77 g HOBT and 2.27g DDC as well as a 4.0 g solution of compound 29 added to THF and the reaction mixture mixed overnight. Work up and cleaning by column chromatography took place analogous to 17. Yield: 85%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-cyano-(D,L) phenylalanine (31)

4.22 g of compound 30 were suspended in a mixture of 35 ml methanol and 15 ml 1 N NaOH and the preparation stirred 6 hours at room temperature. The solution obtained was subsequently mixed with 200 ml water, acidified with 1 N HCl and allowed to stand 10 hours. The precipitate formed was suctioned off, washed with water and dried. Yield: 96%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-cyano-(D,L) phenylalanine-piperidide (32)

2.5 g of compound 31 were dissolved in 30 ml THF, the solution, after cooling down to -18°C, mixed with 0.52 ml NMM and 0.62 cloroformic acid-isobutyl ester and stirred 15 minutes. Thereafter, 0.67 ml piperidine were added, stirred an additional 90 minutes at -18°C and, finally, until reaching room temperature. Work up took place analogous to 11. The raw product obtained was cleaned by column chromatography via silica gel 60 (chloroform/methanol 95:5 as eluting agent). Yield: 86%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-thiocarboxamido-(D,L) phenylalanine-piperidide (33)

0.6 of compound 32 were converted to 10 ml pyridine and 1 ml TEA analogous to 6 and worked up. Yield: 92%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D,L)-piperidide (34)

0.58 g of compound 33 were dissolved in 15 ml acetone, the solution mixed with 0.8 g methyl iodide and refluxed 15 minutes in a water bath. After cooling down, compound 34 was precipitated out through addition of 100 ml ether, suctioned off, washed with ether and dried. Yield: 70%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-(D,L)-piperidide-hydroiodide (35)

0.49 g of compound 34 were converted to 10 ml abs. ethanol with 0.15 g ammonium acetate analogous to 8 and worked up. Yield: 86%, melting point starting at 128°C.

N-α-(2-naphthylsulphonyl)-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-(D,L)-piperidide-hydrochloride (36)

2.0 g of compound 35 were suspended in 300 ml ethyl acetate, the suspension mixed with 40 ml 0.2 N NaOH and extracted. The organic phase was washed with water, dried via Na_2SO_4 and the solvent distilled off. The free base obtained from 35 was dissolved in 10 ml TFA, the solution stirred 2 hours at room temperature and the solvent subsequently distilled off. The residue was mixed with 1 ml 2 N ethyl acetate/HCl and compound 36 precipitated out with ether. The precipitate was suctioned off, washed with ether and dried. Yield: 79%, melting point starting at 155°C.

N-α-(2-naphthylsulphonyl)-β-methoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-(D,L)-piperidide-hydrochloride (37)

0.25 g of compound 36 were converted analogous to 16 and worked up. Yield: 86%, melting point starting at 135°C.

Example 6

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl- and (D,L) aspartyl-4-amidino-(D,L)-phenylalanine (40, 41)

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-thiocarboxamido-(D,L)-phenylalanine (38)

0.7 g of compound 31 were converted to 10 ml pyridine and 1 ml TEA analogous to 6 and worked up. Yield: 93%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanine-hydroidide (39)

0.7 g of compound 38 were converted analogous to 34 and worked up. Yield: 99%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-hydrochloride (40)

0.86 g of the thioimide acid-hydroiodide 39 were converted to 10 ml methanol with 0.3 g ammonium acetate analogous to 8 and worked up. The hydroiodide precipitating out was converted to the hydrochloride by dissolving the compound in 5ml methanol, mixing the solution with 1 ml methanolic hydrochloric acid and immediately precipitating out the hydrochloride with ether. This process was repeated once. The residue formed was suctioned off, washed with ether and dried. Yield: 59%, melting point starting at 168°C.

N-α-(2-naphthylsulphonyl)-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-hydrochloride (41)

0.3 g of compound 40 were dissolved in 4 ml TFA and stirred 5 hours at room temperature. Subsequently,, the solvent was distilled off, the residue dissolved in 5 ml ethanol, 0.5 ml 2 N ethyl acetate/HCl added to the solution and compound 41 precipitated out with ether. The precipitate was suctioned off, washed with ether and dried. Yield: 70%, melting point starting at 112°C.

Example 7

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-, -D,L)-aspartyl- and β-methoxycarbonyl-(D,L) aspartyl-4-amidino-(D,L)-phenylalanine-methyl ester (44-46)

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-thiocarboxamido-(D,L)-phenylalanine-methyl ester (42)

1.5 g of compound 30 were converted to 15 ml pyridine and 1.5 ml TEA analogous to 6 and worked up. Yield: 89%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanine-methyl ester-hydroiodide (43)

1.56 g of compound 42 and 2.0 g methyl iodide were converted to 30 ml acetone analogous to 34 and worked up. Yield: 78%, amorphous product.

N-α-(2-naphthylsulphonyl)-β-t-butoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-methyl ester-hydroiodide (44)

1.5 g of the compound and 0.5 g ammonium acetate were converted to 10 ml methanol analogous to 8 and worked up. Yield: 76%, melting point starting at 126°C.

N-α-(2-naphthylsulphonyl)-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-methyl ester-hydrochloride (45)

0.9 g of compound 44 were suspended in 200 ml ethyl acetate, the suspension mixed with 20 ml 0.2 N NaOH and extracted. The organic phase was washed with water, dried via $MgSO_4$ and the solvent distilled off, whereby 0.7 g of the free base were obtained from 44. The solution was dissolved in 7 ml TFA, stirred 2 hours at room temperature and the solvent subsequently distilled off. The residue was dissolved in 8 ml ethanol, the solution mixed with 1 ml 2 N ethyl acetate/HCl and compound 45 precipitated out with ether. The precipitate was suctioned off, washed with ether and dried. Yield: 77%, melting point starting at 78°C.

N-α-(2-naphthylsulphonyl)-β-methoxycarbonyl-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanine-methyl ester-hydrochloride (46)

0.25 g of compound 45 were dissolved in 5 ml abs. methanol, the solution mixed with 50 drops 2 N methanolic hydrochloric acid and the preparation stored 20 hours at room temperature. Subsequently,, compound 46 was precipitated out with ether, suctioned off, washed with ether and dried. Yield: 78%, melting point starting at 84°C.

Example 8

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-amidino-(D,L)-phenylalanyl-(D)-praline-t-butylester (53)

N-α-(2-naphthylsulphonyl)-(D,L)-leucine (47)

5.0 g (D,L) leucine were dissolved in 200 ml 0.42 M sodium carbonate solution, a solution of 10.4 g 2-naphthylsulphonyl chloride added to 150 ml ether and the preparation stirred 16 hours at room temperature, whereby the sodium salt of compound 47 precipitated out. The precipitate was subsequently suctioned off, washed with ether and, under warming, dissolved in water. The solution was acidified with 1 N HCl, the precipitate formed suctioned off after standing for several hours, washed with water and dried. Yield: 52%, melting point 103-104°C (from ethyl acetate/hexane).

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-cyano-(D,L)-phenylalanine-methyl ester (48)

3.3 g of compound 28, 1.56 ml NMM and 2.16 g HOBT were dissolved in 10 ml DMF, the solution cooled down to 0°C and, under stirring, mixed with a solution of 4.1 g of compound 47 in 30 ml THF and 2.77 g DCC. The reaction mixture was stirred overnight at room temperature and subsequently worked up analogous to 17. Yield: 97%, melting point 105-107°C (from ethyl acetate/hexane).

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-cyano-(D,L)-phenylalanine (49)

6.3 g of compound 48 were dissolved in 50 ml methanol, 25 ml 1 N NaOH added and stirred at room temperature until complete saponification (tf control). Work up and cleaning by column chromatography took place analogous to 18. Yield: 61%, melting point 146-148°C (from methanol/water).

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-cyano-(D,L)-phenylalanyl-(D)-proline-t-butylester (50)

0.68 g (D)-proline-t-butylester, 0.67 g HOBT, 0.82 g DCC and 1.78 g of compound 49 were converted to 25 ml THF analogous to 17 and worked up. Cleaning took place by column chromatography via silica gel 60 (chloroform/methanol 97:3 as eluting agent). Yield: 85%, amorphous product.

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-thiocarboxamido-(D,L)-phenylalanyl-(D)-proline-t-butylester (51)

1.0 g of compound 50 were converted analogous to 6 and worked up. Yield: 95%, amorphous product.

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D)-proline-t-butylester-hydroiodide (52)

1.0 g of compound 51 and 1.1 g methyl iodide were converted to 20 ml acetone analogous to 34 and worked up. Yield: 60%, amorphous product.

N-α-(2-naphthylsulphonyl)-(D,L)-leucyl-4-amidino-(D,L)-phenylalanyl-(D)-proline-t-butylester-hydroiodide (53)

0.67 g of compound 52 were dissolved in 10 ml methanol, the solution mixed with 0.1 g ammonium acetate and the preparation heated gently 3 hours at 60°C in a water bath. The solvent was subsequently distilled off, the residue dissolved in a little methanol and compound 53 precipitated out with ether. Yield: 65%, melting point starting at 150°C.

Example 9

N-α-(2-naphthylsulphonyl)-glycl-4-amidino-(D,L)-phenylalanine-4-methyl piperide (57)

N-α-(2-naphthylsulphonyl)-glycl-4-cyano-(D,L)-phenylalanine-4-methyl piperide (54)

0.9 g 4-methyl piperidine, 1.4 g HOBT, 1.71 g DCC and 1.94 g of compound 10 were converted to 34 ml THF analogous to 17 and worked up. Cleaning took place by column chromatography via silica gel 60 (chloroform as eluting agent). Yield: 84%, melting point 202-203°C (from ethyl acetate/hexane).

N-α-(2-naphthylsulphonyl)-glycl-4-thiocarboxamido-(D,L)-phenylalanine-4-methyl piperide (55)

1.85 g of compound 54 were converted to 20 ml pyridine and 1.5 ml TEA analogous to 6 and worked up, whereby a solid product was obtained. 25 ml methanol were added, compound 55 suctioned off, washed with methanol and dried. Yield: 95%, melting point 235-236°C.

N-α-(2-naphthylsulphonyl)-glycl-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanine-4-methyl piperide-hydroiodide (56)

1.8 g of the thioamide 55 were dissolved in 3 ml DMF under warming, 100 ml acetone and 6 g methyl iodide added and the preparation stored, protected from the light, 16 hours at room temperature. It was subsequently poured into 250 ml ether, the precipitate formed suctioned off, washed with ether and dried. Yield: 85%, amorphous powder.

N-α-(2-naphthylsulphonyl)-glycl-4-amidino-(D,L)-phenylalanine-4-methyl piperide-hydroiodide (57)

1.2 g of compound 54 were dissolved in 30 ml methanol, the solution mixed with 0.21 g ammonium acetate and warmed gently 3 hours in a water bath, whereby a precipitate developed after a short time, which gradually dissolved again. The solvent was subsequently distilled off, the residue dissolved in abs. ethanol and compound 57 precipitated out with ether. The precipitate was suctioned off, washed with ether and dried. Yield: 78%, melting point 198-204°C (sinter beforehand).

Example 10

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -methyl ester (62, 63)

N-α-(2-naphthylsulphonyl)-4-cyano-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -methyl ester (58)

2.2 g (D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-methyl ester and 1.1 g NMM were dissolved in 20 ml ethyl acetate, a 4.0 g solution of the acid chloride obtained from compound 3 and thionyl chloride added dropwise in 50 ml ethyl acetate to the reaction mixture and stirred 2 hours at room temperature. The solvent was subsequently distilled off, the residue dissolved in 20 ml methanol and allowed to stand to crystallize. The precipitate formed was suctioned off, washed with methanol and dried. Yield: 65%, melting point 169-173°C.

N-α-(2-naphthylsulphonyl)-4-cyano-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid (59)

2.0 g of compound 58 were suspended in a mixture of, in each case, 20 ml 1 N NaOH and methanol and stirred at room temperature until complete saponification, whereby after a short time a clear solution was obtained. Subsequently,, half of the solvent was distilled off, 100 ml water added and acidified with 1 N HCl. After to the reaction mixture several hours, the precipitate formed was suctioned off, washed with water and dried. Yield: 93%, amorphous product.

N-α-(2-naphthylsulphonyl)-4-thiocarboxamido-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid (60)

1.3 g of compound 59 were converted to 20 ml pyridine and 1.5 ml TEA analogous to 6 and worked up. Yield: 98%, amorphous product.

N-α-(2-naphthylsulphonyl)-4-S-methyl iminothiocarbonyl-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-hydroiodide (61)

1.3 g of the thioamide 60 were dissolved in 20 ml acetone, the solution mixed with 4.0 g methyl iodide and stored, protected from the light, 16 hours at room temperature. The solution was subsequently poured into 200 ml ether, the precipitate formed suctioned off, washed with ether and dried. Yield: 86%, amorphous powder.

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-hydrochloride (62)

1.14 g of compound 61 were dissolved in 40 ml methanol, the solution mixed with 0.19 g hydroxyl ammonium acetate and the reaction mixture stirred 20 minutes at room temperature. Subsequently,, a solution of 0.145 g $NaHCO_3$ in water was added, approximately 20 ml solvent distilled out and 50 ml water added. After 3-days' storage in the refrigerator, the crystallized betain of compound 62 suctioned off, washed with water and dried. Yield: 64%, melting point 162-178°C.

The conversion to the hydrochloride took place as described under 15. Yield: 92%, melting point starting at 165°C.

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-methyl ester-hydrochloride (63)

0.3 g of compound 62 were dissolved in 7.5 ml abs. methanol, 40 drops 3 N methanolic hydrochloric acid added and the preparation allowed to stand 30 hours at room temperature. Subsequently,, half of the solvent was distilled off, compound 63 precipitated out with ether, suctioned off, washed with ether and dried. Yield: 86%, melting point starting at 90°C.

Example 11

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid (65) and -ethyl (64) and -methyl ester (66)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-ethyl ester-hydrochloride (64)

2.0 g of compound 4 were dissolved in a mixture of, in each case, 15 ml dioxane and methanol, 20 ml ethanolic ammonia solution added and hydrated in the presence of Raney nickel catalyst under normal conditions. After complete hydration (tf control), the solution was filtered off, the solvent distilled off and the oily residue dissolved in a little ethanol. The solution obtained was acidified with 2 N ethyl acetate/HCl and compound 64 precipitated out with ether, whereby the product became solid only after prolonged standing. The precipitate was suctioned off, washed with ether and dried. Yield: 58%, melting point starting at 115°C.

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-hydrochloride (65)

1.14 g of compound 64 were suspended in a mixture of, in each case, 12 ml 1 N NaOH and methanol and the preparation stirred at room temperature until complete saponification. The solution obtained was subsequently acidified with 3 N HCl and the solvent distilled off in the vacuum. To remove the remaining water, the solution was codistilled 2 times with isopropanol/toluol 1:1. The solid residue was extracted with 40 ml abs. ethanol, filtered off from undissolved NaCl and compound 65 precipitated out

of the filtrate after evaporation to low bulk with ether. The precipitate was suctioned off, washed with ether and dried. Yield: 75%, melting point starting at 155°C.

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-methyl ester-hydrochloride (66)

0.32 g of compound 65 were dissolved in 10 ml abs. methanol, the solution mixed with 2 ml 3 N methanolic hydrochloric acid and allowed to stand 20 hours at room temperature. Subsequently,, compound 66 was precipitated out through addition of ether, the precipitate formed suctioned off, washed with ether and dried. Yield: 85%, melting point, starting at 130°C.

TABLE OF ELEMENTARY ANALYSES and DC DATA

NO.	FORMULA	M.G.		C	H	N	S	DC R_f(LS)
3	$C_{20}H_{16}N_2O_4S$	380.426	Range	63.15	4.24	7.36	8.43	0.32 (2)
			Gradient	63.40	4.48	7.66	8.30	
4	$C_{28}H_{29}N_3O_5S$	519.625	Range	64.76	5.63	8.09	6.17	0.83 (2)
			Gradient	64.46	5.85	8.09	6.45	
5	$C_{26}H_{25}N_3O_5S \cdot H_2O$	509.587	Range	61.28	5.34	8.24	6.29	0.56 (2)
			Gradient	61.17	5.01	8.11	6.66	0.53
8	$C_{26}H_{29}N_4O_5S\cdot$ HI	636.515	Range	49.06	4.59	8.80	5.04	0.39 (1)
			Gradient	49.48	4.92	9.01	5.28	
10	$C_{22}H_{18}N_3O_5S$	436.471	Range	60.54	4.16	9.63	7.35	0.12 (2)
			Gradient	60.27	4.31	9.23	7.48	
11	$C_{29}H_{34}N_4O_5S$	566.683	Range	61.47	6.05	9.89	5.66	0.65 (2)
			Gradient	61.93	5.96	9.73	5.67	
15 H	$C_{25}H_{27}N_5O_6S\cdot$ HCl $_2O$	580.067	Range	51.77	5.21	12.07	5.53	0.17 (1)
			Gradient	51.31	5.50	11.81	5.40	
16 H	$C_{26}H_{29}N_5O_6S\cdot$ HIS $_2O$	594.094	Range	52.57	5.43	11.79	5.40	0.27 (1)
			Gradient	52.03	5.74	11.56	5.52	
17	$C_{30}H_{32}N_4O_6S$	576.678	Range	62.48	5.59	9.72	5.56	0.79 (2)
			Gradient	62.48	5.86	9.68	5.80	
18	$C_{28}H_{28}N_4O_6S$	548.624	Range	61.30	5.14	10.21	5.84	0.50 (2)
			Gradient	61.11	5.46	10.14	5.75	0.39
21	$C_{28}H_{32}N_5O_6S\cdot$ HI	693.568	Range	48.49	4.65	10.10	4.62	0.24 (1)
			Gradient	48.83	4.88	10.43	4.93	
22	$C_{30}H_{32}N_4O_6S$	576.678	Range	62.48	5.59	9.72	5.56	0.75 (2)
			Gradient	62.24	5.88	10.04	5.60	
23	$C_{28}H_{28}N_4O_6S$	548.624	Range	61.30	5.14	10.21	5.84	0.49 (2)
			Gradient	61.14	5.23	9.81	6.20	
26 H	$C_{28}H_{31}N_5O_6S\cdot$ HCl $_2O$	620.132	Range	54.23	5.53	11.29	5.17	0.20 (1)
			Gradient	54.04	5.48	11.12	5.02	

NO.	FORMULA	M.G.		C	H	N	S	DC R_f(LS)
27	$C_{29}H_{33}N_5O_6S \cdot HCl$	634.159	Range	54.93	5.72	11.04	5.06	0.26 (1)
	$\cdot H_2O$		Gradient	54.76	5.83	11.04	4.96	
29	$C_{18}H_{21}NO_6S$	379.437	Range	56.98	5.58	3.69	8.45	0.40 (2)
			Gradient	56.49	5.38	3.67	8.51	
30	$C_{29}H_{31}N_3O_7S$	565.652	Range	61.58	5.52	7.43	5.67	0.78 (2)
			Gradient	61.48	5.90	7.68	5.64	
31	$C_{28}H_{29}N_3O_7S$	569.641	Range	59.04	5.49	7.38	5.63	0.27 (2)
	$\cdot H_2O$		Gradient	58.76	5.25	7.26	5.86	
32	$C_{33}H_{38}N_4O_6S$	618.759	Range	64.06	6.19	9.05	5.18	0.79 (2)
			Gradient	63.78	6.41	8.92	5.30	
35	$C_{33}H_{41}N_5O_6S \cdot HI$	781.719	Range	50.70	5.67	8.96	4.10	0.43 (1)
	$\cdot H_2O$		Gradient	50.31	5.64	9.07	4.40	
36	$C_{29}H_{33}N_5O_6S \cdot HCl$	616.143	Range	56.53	5.56	11.37	5.20	0.23 (1)
			Gradient	56.94	5829	11.21	5.44	
37	$C_{30}H_{35}N_5O_6S \cdot HCl$	630.170	Range	57.18	5.76	11.11	5.09	0.32 (1)
			Gradient	57.49	5.72	11.03	5.41	
40	$C_{28}H_{32}N_4O_7S \cdot HCl$	605.117	Range	55.58	5.50	9.26	5.30	0.33 (1)
			Gradient	54.91	5.44	9.55	5.76	
41	$C_{24}H_{24}N_4O_7S \cdot HCl$	576.033	Range	50.05	4.90	9.73	5.57	0.18 (1)

	$\cdot H_2O$		Gradient	50.07	5.09	9.84	5.54	
44	$C_{29}H_{34}N_4O_7S \cdot HI$	710.596	Range	49.02	4.96	7.88	5.41	0.53 (1)
			Gradient	49.26	5.14	7.78	4.92	
45	$C_{25}H_{26}N_4O_7S \cdot HCl$	563.036	Range	53.33	4.83	9.95	5.69	0.31 (1)
			Gradient	53.42	4.61	9.75	5.63	
46	$C_{26}H_{28}N_4O_7S \cdot HCl$	577.063	Range	54.21	4.90	9.73	5.57	0.41 (1)
			Gradient	53.76	5.05	9.91	5.95	
47	$C_{16}H_{19}NO_4S$	321.399	Range	59.79	5.96	4.36	9.98	0.48 (2)
			Gradient	59.77	5.89	4.64	9.89	
48	$C_{27}H_{29}N_3O_5S$	507.614	Range	63.89	5.76	8.28	6.32	0.73 (2)
				63.84	5.90	8.15	6.39	
49	$C_{26}H_{27}N_3O_5S$	493.587	Range	63.27	5.51	8.51	6.50	0.30 (2)
			Gradient	62.29	5.54	8.40	6.61	
50	$C_{35}H_{42}N_4O_6S$	646.813	Range	65.00	6.55	8.66	4.96	0.79 (2)
			Gradient	65.20	6.84	8.54	5.39	
53	$C_{35}H_{45}N_5O_6S \cdot HI$	791.757	Range	53.10	5.86	8.85	4.05	0.46 (1)
			Gradient	52.93	5.99	8.71	4.22	
54	$C_{28}H_{30}N_4O_4S$	518.640	Range	64.84	5.83	10.80	6.18	0.79 (2)
			Gradient	65.00	6.15	11.28	6.40	
57	$C_{28}H_{33}N_5O_4S \cdot HI$	663.584	Range	50.68	5.16	10.55	4.83	0.53 (1)
			Gradient	50.37	5.21	10.35	5.20	

58	$C_{31}H_{27}N_3O_5S$	553.642	Range	67.25	4.92	7.59	5.79	0.83 (2)
			Gradient	67.44	5.13	7.72	5.44	
59	$C_{30}H_{25}N_3O_5S \cdot H_2O$	557.631	Range	64.62	4.88	7.54	5.75	0.56 (2)
			Gradient	65.08	5.12	7.87	5.45	0.52
62	$C_{30}H_{28}N_4O_6S \cdot HCl \cdot H_2O$	627.123	Range	57.46	5.13	8.93	5.11	0.65 (1)
			Gradient	57.22	5.17	8.67	5.40	
63	$C_{31}H_{30}N_4O_6S \cdot HCl \cdot H_2O$	641.150	Range	58.07	5.19	8.74	5.00	0.83 (1)
			Gradient	58.05	5.09	8.37	5.16	
64	$C_{28}H_{33}N_3O_5S \cdot HCl \cdot H_2O$	578.134	Range	58.17	6.28	7.27	5.55	0.33 (1)
			Gradient	57.90	6.03	7.05	5.82	
65	$C_{26}H_{29}N_3O_5S \cdot HCl \cdot H_2O$	550.080	Range	56.77	5.86	7.64	5.83	0.27 (1)
			Gradient	56.86	5.83	7.44	6.10	
66	$C_{27}H_{32}N_3O_5S \cdot HCl$	564.107	Range	57.49	6.08	7.45	5.68	0.34 (1)
			Gradient	57.43	5.74	7.38	5.92	

Overview of further compounds synthesized in accordance with the previously indicated production methods not listed in the Examples 1-11:

N-α-(2-naphthylsulphonyl)-γ-t-butoxy-(D,L)-glutamyl-4-amidino-(D,L)-phenylalanine (68)

N-α-(2-naphthylsulphonyl)-γ-t-butoxy-(D,L)-glutamyl-4-amidino-(D,L)-phenylalanyl-piperide (69)

N-α-(2-naphthylsulphonyl)-(D,L), asparagyl-4-amidino-(D,L)-phenylalanyl-(D)-proline-t-butyl ester (70)

N-α-(2-naphthylsulphonyl)-β-t-butoxy-(D,L)-aspartyl-4-amidino-(D,L)-phenylalanyl(D)-proline (71)

N-α-(2-naphthylsulphonyl)-(D,L)-glutaminyl-4-amidino-(D,L)-phenylalanine (72)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanine (73)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-(L)-phenylglycine (74)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-(L)-phenylglycine-methyl ester (75)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-(L)-phenylglycine-t-butyl ester (76)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-(L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid (77)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-4-methyl-(D,L)-pipecolic acid (78)

N-α-(2-naphthylsulphonyl)-glcyl-4-amidino-(D,L)-phenylalanyl-4-methyl-(D,L)-pipecolic acid-methyl ester (79)

N-α-(2-naphthylsulphonyl)-glcyl-4-oxamidino-(D,L)-phenylalanyl-4-methyl piperidide (80)

N-α-(2-naphthylsulphonyl)-glcyl-4-oxamidino-(D,L)-phenylalanyl-isonipecotine acid (81)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanine (82)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanine-4-methyl piperidide (83)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-isonipecotine acid (84)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-isonipecotine acid-methyl ester (85)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid (86)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-piperide-2-on-carboxylic acid (87)

N-α-(2-naphthylsulphonyl)-(D,L)-phenylalanyl-4-methyl-(D,L)-pipecolic acid (88)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-nipecotine acid (89)

N-α-(2-naphthylsulphonyl)-4-amidino-(D,L)-phenylalanyl-nipecotine acid-methyl ester (90)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-nipecotine acid (91)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-nipecotine acid-methyl ester (92)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-(D,L)-pipecolic acid (93)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-(D,L)-pipecolic acid-methyl ester (94)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-isonipecotine acid (95)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanyl-isonipecotine acid-methyl ester (96)

N-α-(2-naphthylsulphonyl)-4-oxamidino-(D,L)-phenylalanine-4-methyl piperidide (97)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-nipetocine acid-ethyl ester (98)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-nipetocine acid (99)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-nipetocine acid-methyl ester (100)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-nipetocine acid-n-butyl ester (101)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-pipecolic acid-ethyl ester (102)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-pipecolic acid-n-butyl ester (103)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-isonipecotine acid-ethyl ester (104)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-isonipecotine acid (105)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-isonipecotine acid-methyl ester (106)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-isonipecotine acid-n-butyl ester (107)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)- 1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-methyl ester (108)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)- 1,2,3,4-tetrahydroisochinoline-3-carboxylic acid (109)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-ethyl ester (110)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-(D,L)-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid-n-butyl ester (111)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(D,L)-phenylalanyl-4-methyl piperidide (112)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(L)-phenylalanyl-(D)-proline-t-butyl ester (113)

N-α-(2-naphthylsulphonyl)-4-aminomethyl-(L)-phenylalanyl-(D)-proline (114)

To be cited as examples of the general formula I with para-position basic grouping (R1 = (a) to (e)), unless not already listed, are:

<u>N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-</u>

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-glycyl

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-alanyl and -β-alanyl

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-leucyl

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-aspartyl- and β-alkoxy-aspartyl-

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-asparaginyl-

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-glutamyl-and γ-alkoxy-glutamyl-

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

N-α-(tosyl)- and (1- or 2-naphthylsulphonyl)-glutaminyl-

phenylalanine-alkyl, arakyl and aryl esters

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-pyrrolidides

phenylalanine-alkyl, hydroxyalkyl- and hydroxy-piperidides

phenylalanine-N-alkyl-, N-aryl- and N-alkoxy carbonyl-piperazides

phenylalanyl-proline and -hydroxyproline and -alkyl-, arakyl and aryl esters

phenylalanyl-piperidine-2-, 3- or 4-carboxylic acid and their -alkyl-, arakyl and aryl esters

phenylalanyl-alkyl-piperidine-2-, 3- or 4-carboxylic acids and their -alkyl-, arakyl and aryl esters

phenylalanyl-1,2,3,4-tetrahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-3-carboxylic acid and -alkyl-, arakyl and aryl esters

phenylalanyl-decahydroisochinoline-4-carboxylic acid and -alkyl-, arakyl and aryl esters

The compounds listed can be present as racemates and, following corresponding separation, as pure enantiomers and/or diastereomers.

The biological properties of representative compounds in accordance with the invention are listed in the following:

In Table 1, inhibition of clotting enzymes thrombin and trypsin by the compounds cited is indicated by the dissociation constant K_i (expressed in µmol/l). All compounds examined competitively inhibit the substrate separation effected by both enzymes. Among the 4-amidino phenylalanine derivates listed in Table 1 a series of compounds with high antithrombin activity, i.e., with K_i values below 1 µmol/l, is found. Thrombin inhibition is comparatively stronger than inhibition by trypsin. K_i values for trypsin inhibition usually lie on an order of magnitude of 1 to 2 times higher than those for thrombin inhibition.

The compounds derived from 4-oxamido phenylalanine and 4-aminomethyl phenylalanine produce lower antithrombin activity; some of them, however, have usable K_i values for thrombin inhibition in the micromolar range.

Abbreviations in Tables 1 and 2:

for R^1, Am = amidino, Ox = oxamidino, AMe = aminomethyl

for R^2, Ppd = piperidide, Ppd(4-Me) = 4-methylpiperidide, OH = carboxylic acid, OMe = methyl ester, OEt = ethyl ester, OnBu = n-butyl ester, OtBu = t-butyl ester, Pro = proline, Pip-OH = pipecolic acid, iNip-OH = isonipecotine acid, Nip-OH = nipecotine acid, Sar-OH, sarcosine, Tic-OH = 1,2,3,4-tetrahydroisochinoline-3-carboxylic acid, Phg-OH = phenyl-glycine, Pip(4-Me) = 4-methyl-D,L-pipecoine acid, 2-Ppn-3-COOH = piperide-2-on-3-carboxylic acid

for R^4, Na = 2-naphthyl

Table 1

Inhibition of thrombin and trypsin by Na-protected 4-substituted phenylalanine derivates

Compound	R^1	R^2	n	R^3	R^4	K_i [µmol/l] Thrombin	Trypsin
NAPAP	Am	Ppd	1	H	Na	0.006	0.69
36	Am	Ppd	1	CH_2CO-OH	Na	0.45	7.5
41	Am	OH	1	CH_2CO-OH	Na	640	300
45	Am	OMe	1	CH_2CO-OH	Na	60	107
37	Am	Ppd	1	CH_2CO-OMe	Na	0.24	5.9
46	Am	OMe	1	CH_2CO-OMe	Na	7.1	27
35	Am	Ppd	1	CH_2CO-OtBu	Na	0.47	12
40	Am	OH	1	CH_2CO-OtBu	Na	17	66
44	Am	OMe	1	CH_2CO-OtBu	Na	3.8	46
70	Am	D-Pro-OtBu	1	CH_2CO-NH_2	Na	0.51	85
69	Am	Ppd	1	$(CH_2)_2CO$-OtBu	Na	0.53	3.4
53	Am	D-Pro-OtBu	1	$CH_2CH(CH_3)_2$	Na	0.56	55
57	Am	Ppd (4-Me)	1	H	Na	0.0016	0.06
26	Am	iNip-OH	1	H	Na	2.0	2.6
27	Am	iNip-OMe	1	H	Na	0.29	0.71
15	Am	Sar-OH	1	H	Na	5.9	6.5
16	Am	Sar-OH	1	H	Na	0.19	0.9
21	Am	D,l-Pip-OH	1	H	Na	1.4	4.3
80	Ox	Ppd (4-Me)	1	H	Na	48	230
8	Am	D,l-Pip-OH	0	-	Na	5.8	34
83	Am	Ppd (4-Me)	0	-	Na	0.34	10.4
84	Am	iNip-OH	0	-	Na	170	160
85	Am	iNip-OMe	0	-	Na	3.2	3.1
89	Am	Nip-OH	0	-	Na	34	120
90	Am	iNip-OMe	0	-	Na	0.68	16

Table 1 (cont.)

Compound	R^1	R^2	n	R^3	R^4	K_i [µmol/l] Thrombin	Trypsin
113	AMe	Ppd (4-Me)	0	-	Na	2.5	11
106	AMe	iNip-OH	0	-	Na	140	62
107	AMe	iNip-OMe	0	-	Na	33	2.2
100	AMe	Nip-OH	0	-	Na	50	41
101	AMe	Nip-OMe	0	-	Na	3.9	30
65	AMe	D,L-Pip-OH	0	-	Na	47	160
66	AMe	D,L-Pip-OMe	0	-	Na	1.3	82
109	AMe	D,L-Tic-OMe	0	-	Na	42	140
110	AMe	D,L-Tic-OH	0	-	Na	90	41
98	Ox	Ppd (4-Me)	0	-	Na	2.5	180
96	Ox	iNip-OH	0	-	Na	410	350
97	Ox	iNip-OMe	0	-	Na	4.8	530
92	Ox	Nip-OH	0	-	Na	190	430
93	Ox	Nip-OMe	0	-	Na	28	400
94	Ox	D,L-Pip-OH	0	-	Na	19	340
95	Ox	D,L-Pip- OMe	0	-	Na	2.2	330
62	Ox	D,L-Tic-OH	0	-	Na	3.2	200
63	Ox	D,L-Tic-OMe	0	-	Na	22	97

The inhibition effect of some representative compounds in accordance with the invention vis-à-vis factor X_a and factor XII_a, protein C_a, plasmin, plasma kallikrein, tPA and glandular kallikrein is illustrated in Table 2. The inhibition of other enzymes is usually substantially weaker, for example, protein C_a, plasmin, plasma kallikrein and factor X_a (K_i 2 orders of magnitude greater). Vis-à-vis factor XII_a, tPA and glandular kallikrein the derivates are practically ineffective. For the majority of the compounds, therefore, one can speak of selective thrombin inhibitors.

Table 2

Inhibition of thrombin, trypsin, plasmin, factor X_a, factor XII_a, protein C_a, tPA, plasma and glandular kallikrein

						K_1 [µmol/l								
									Factor	Factor	Protein		Gland.	Plasma
Compound	R^1	R^2	n	R^3	R^4	Thrombin	Trypsin	Plasmin	Xa	XIIa	Ca	tPA	Kallikrein	
NAPAP	Am	Ppd	1	H	Na	0.006	0.69	30	7.9	500	4.8	70	93	5.6
36	Am	Ppd	1	CH_2CO-OH	Na	0.45	7.5	260	4.8	25	270	6.6	>1000	47
37	Am	Ppd	1	CH_2CO-OMe	Na	0.24	5.9	170	2.2	34	39	13	1000	33
35	Am	Ppd	1	CH_2CO-OtBu	Na	0.47	12	190	105	>1000	210	670	200	90
44	Am	OMe	1	CH_2CO-OtBu	Na	3.8	46	110	85	330	310	180	69	5.0
57	Am	Ppd (4-Me)	1	H	Na	0.0015	0.06	25	22	>1000	5.1	530	170	14
26	Am	1N1p-OH	1	H	Na	2.0	2.6	240	61	>1000	87	630	>1000	51
27	Am	1N1p-OMe	1	H	Na	0.29	0.71	16	67	>1000	7.0	500	130	20
15	Am	Sar-OH	1	H	Na	5.9	6.5	87	31	700	620	29	730	12

16	Am	Sar-OMe	1	H	Na	0.19	0.9	15	13	40	6.8	26	200	37
83	Am	Ppd (4-Me)	0	-	Na	0.34	10.4	70	31	>1000	310	>1000	130	190
90	Am	N1p-OMe	0	-	Na	0.68	16	180	26	>1000	890	>1000	19	160
113	AMe	Ppd(4-Me)	0	-	Na	2.5	11	75	47	>1000	930	>1000	500	400
101	AMe	Nip-OMe	0	-	Na	3.9	30	13	80	>1000	>1000	>1000	400	>1000
66	AMe	D_1L-Pip-OMe	0	-	Na	1.3	82	234	17	>1000	290	>1000	240	>1000
98	Ox	Ppd(4-Me)	0	-		2.5	180	>1000	140	>1000	>1000	>1000	320	150
97	Ox	1Nip-OMe	0	-	Na	4.8	530	>1000	270	>1000	>1000	>1000	530	>1000
95	Ox	D_1L-Pip-OMe	0	-	Na	2.2	330	540	39	>1000	>1000	>1000	890	>1000
62	Ox	D_1L-Pic-OH	0	-	Na	3.2	200	>1000	120	>1000	>1000	>1000	470	>1000

In comparison to derivates of amino acids containing benzamidine (LD_{50} 10 - 50 mg/kg after intravenous application) tested earlier, the toxicity of the compounds in accordance with the invention is distinctly lower. Thus, for example, for compound 26 a LD_{50}-value of 210 mg/kg following intravenous application was found.

Table 3 summarizes the results of the tests of the pharmacokinetics of two compounds in accordance with the invention and as a comparison thereto, the values with NAPAP. The compounds were administered subcutaneously and perorally in rats. After administration, blood samples were taken at time intervals from 2 to a maximum of 360 minutes from the test animals in which the blood level of the compound to be tested was determined by means of HPLC.

Table 3

Concentration (ng/ml) of the selected compounds in rat plasma following subcutaneous (5 mg/kg) and peroral (100 mg/kg) administration (see also Illustration 2).

Time (min)	NAPAP s.c.	NAPAP p.o.	Compound 26 s.c.	Compound 26 p.o.	Compound 36 s.c.
15	294	0	1344	1867	260
30	375	0	2023	1584	590
45	324	0	2072	848	596
60	361	0	1859	537	551
90	330	0	1541	301	431
120	327	0	1437	235	363
180	230	0	1297	189	259
240	173	-	1095	184	201
300	-	-	936	201	185
360	-	-	184	206	-

In comparison to NAPAP, derivate 26 tested exhibited improved pharmacokinetic behavior. After subcutaneous, administration relatively high, long-lasting blood levels were found. After oral administration, NAPAP cannot be detected in the plasma, while the compounds in accordance with the invention tested by way of example reach relatively high concentrations.

In vitro, a series of representative compounds in accordance with the invention are effective as anticoagulants. In all cases, thrombin time (TT) was most effectively lengthened. This corresponds to the selectivity of these inhibitors which, among clotting factors, inhibit thrombin the most strongly. A prolongation of activated partial thromboplastin time (aPTT), in which, besides thrombin, the enzymes involved in the early phase of coagulation come to bear, is achieved through higher concentration of the inhibitors. This also applies to the influencing of prothrombin time (PT), which represents the extrinsic coagulation path. That is shown in an exemplary manner for compound 57 in Ill. 1.

Expediently, the phenylalanine derivates produced according to one of the methods in accordance with the invention are converted as such or as salts with a physiologically compatible inorganic or organic acid using suitable pharmaceutical adjuvant substances. In conformity with the pharmacokinetic behavior, these are, in particular, transdermal therapy systems like patches, but also tablets, dragées, capsules, suppositories, solutions, etc.

Dosaging depends on antithrombin effectiveness, toxicity, possible blood level values, bioavailability and kind of application of the compound in accordance with the invention used and, very generally, on the blood values, weight and general condition of the patient, such that dosaging must, in the final analysis, be determined by the practicing physician. In principle, dosaging corresponds to that of known thrombin-inhibiting compounds and lies between approximately 0.2 mg/kg and approximately 20 mg/kg body weight, whereby, if applicable, higher doses can also be administered. For an adult patient, therefore, daily doses of a compound in accordance with the invention from approximately 50 mg to approximately 1600 mg or more, result.

With the aid of compound 26 the conversion into 4 pharmaceutical forms of administration shall be shown by way of example.

Example 1

Tablets with 100 mg of compound 26 as active ingredient

Composition:

1 tablet contains 100 mg active ingredient, 60 mg lactose, 30 mg wheat starch and 1 mg magnesium stearate.

Production method

The active ingredient mixed with lactose and wheat starch is uniformly thoroughly moistened with a 20% ethanolic solution of polyvinyl pyrrolidone, pressed through a 1.5 mm mesh sieve and dried at 40°C. The granulate obtained in this manner is mixed with magnesium stearate and pressed into tablets.

Example 2

Dragées with 50 mg of compound 26 as active ingredient

Composition:

1 dragée contains 50 mg active ingredient, 30 mg lactose, 15 mg wheat starch.

Production method

The active ingredient mixed with lactose and wheat starch is granulated in the manner described under Example 1 and pressed into oval tablet cores which are subsequently made into dragées. For the dragée-forming process, a sugar mixture, consisting of 48 g powdered sugar, 18 g gum arabic, 48 g wheat starch and 4 g magnesium stearate and, as binder, a mixture of equal parts mucilago gums arabic and water are used.

Example 3

Suppositories with 100 mg of compound 26 as active ingredient

Composition:

1 suppository contains 100 mg active ingredient and 0.9 g cetylphthalate as base.

Production method

1.0 g of the finely pulverized active ingredient are triturated with twice the amount of the liquefied base. The trituration is proportionately mixed with the remainder of the liquefied base and worked to uniform constitution. In the vicinity of pourability, the mixture is poured into a suitable mold and allowed to stand until cool.

Example 4

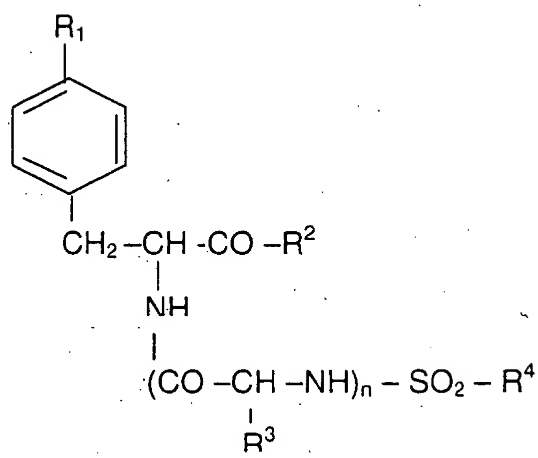
Injection or injection solution with 10 mg/ml of compound 26 as active ingredient

Production method

1.0 g active ingredient are dissolved ad injectionem in 100 ml aqua, the solution filtered and, if applicable, bottled in 2 ml ampoules. The vessels filled with the active ingredient solution and sealed are subjected to vapor sterilization at 121 to 124°C.

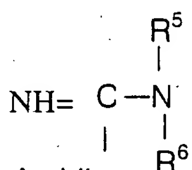
PATENT CLAIMS

1. D,L-, L- and D-phenylalanine derivates of the formula

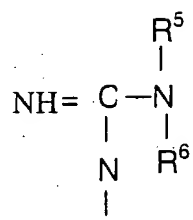
I 

in which

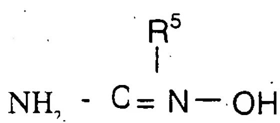
R^1 represents a basic group of the formula

(a) 

Amidino

(b) 

Guanidino

(c) 

Oxamidino

(d) $-CH_2-NH_2$

Aminomethyl

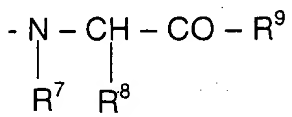
or (e) $-NH_2$

Amino

wherein, R^5 and R^6, in the formulas (a) and (b), designate in each case a hydrogen or a straight-chain or branched low alkyl group,

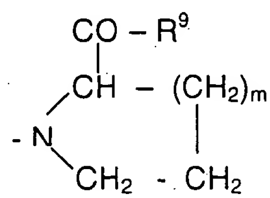
R^2 (f) is OH, O-alkyl, O-cycloalkyl, O-aralkyl,

(g) represents a group of the formula



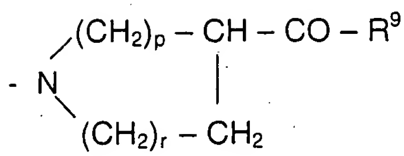
in which R^7 designates hydrogen or a straight-chained or branched low alkyl group and R^8 a straight-chained or branched low alkyl group, a 1- or 2-hydroxyethyl group, a methyl mercapto ethyl group, an aminobutyl group, a guanidino propyl group, a carboxy (low) alkyl group, a phenyl (low) alkyl group, whose ring, if applicable, is substituted by OH, halogen, low alkyl or methoxy, a cyclohexyl or cyclohexyl methyl group, whose ring, if applicable, is substituted by OH, halogen, low alkyl or methoxy, or an N-heteroaryl (low) alkyl group with 3 to 8 carbon atoms in the heteroaryl, e.g., imidazolyl methyl or indolyl methyl, wherein the group (g) is racemic or D- or L-configured,

(h) represents a group of the formula



in which m designates the number 1 or 2 and in which one of the methylene groups is possibly substituted by a hydroxyl, carboxyl, low alkyl or aralkyl group, wherein the group (h) is racemic or D- or L-configured,

(i) represents a group of the formula



in which p = r = 1, p = 1 and r = 2 or p = 2 and r = 1 and in which one of the methylene groups is possibly substituted by a hydroxyl, carboxyl, low alkyl or aralkyl group,

(k) represents a piperidyl group which is possibly substituted in one of the positions 2, 3 and 4 by low alkyl, hydroxyalkyl or hydroxy group,

wherein a further aromatic or cycloaliphatic ring, preferably phenyl or cyclohexl, is fused to the heterocycloaliphatic rings of the formulas (h), (i), (k) in the 2,3 or 3,4 position, referenced to the heteroatom,

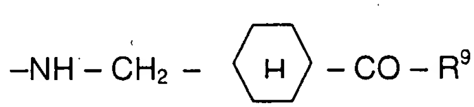
(l) a piperazyl group, which is possibly substituted in p-position by an alkyl group, a aryl group or an alkoxycarbonyl group,

(m) represents a group of the formula

$$-\underset{\displaystyle R^{10}}{\overset{|}{N}} - (CH_2)_{n'} - CO - R^9$$

in which n' designate the numbers 1 through 6 and r10 hydrogen or the methyl or cyclohexyl group and R^1 is = (b) to (e),

(n) represents a group of the formula



wherein R^9 designates in the formulas (g), (h), (i), (l), (m) and (n) a hydroxyl, straight-chained or branched low alkoxy, cycloalkoxy or an aralkoxy group,

or

(o) represents a combination from 2 to 20, preferably 2 to 5, in particular 2 or 3, of the derived groups defined under (g), (h), (i), (k), (l), (m) and (n), linked together by amide bonds (R^9 = single bond), wherein the C-terminal group is possibly coupled to a group R^9,

R^3 represents hydrogen or straight-chained or branched low alkyl, aralkyl, carboxyalkyl, alkoxycarbonyl-alkyl-, carboxamido-alkyl-, heteroarylalkyl- or a 1- or 2-hydroxyethyl group, wherein n designates the number 0 or 1 and the amino acid possibly inserted is racemic or D- or L-configured, and

R^4 represents an aryl group, e.g. phenyl, methylphenyl, α- or β-naphthyl or 5-dimethylamino)-naphthyl, or a heteroaryl group, e.g. quinolyl,
whereby low represents 1-4 carbon atoms,

and their salts with mineral acids or organic acids.

2. Phenylalanine derivates in accordance with patent claim 1, in which

R^2 is O-alkyl, O-cycloalkyl or aralkyl if n=0, represents a heterocycloaliphatic group explained in greater detail in the formulas (h), (i), (k) and (l),

R^4 designates β-naphthyl and

n means the number 1, if R^2 is different from O-alkyl, O-cycloalkyl or aralkyl.

3. Utilization of the phenylalanine derivates in accordance with patent claim 1 or 2 for the production of orally, anally, subcutaneously or intravenously administered, antithrombotically active pharmaceutical preparations .

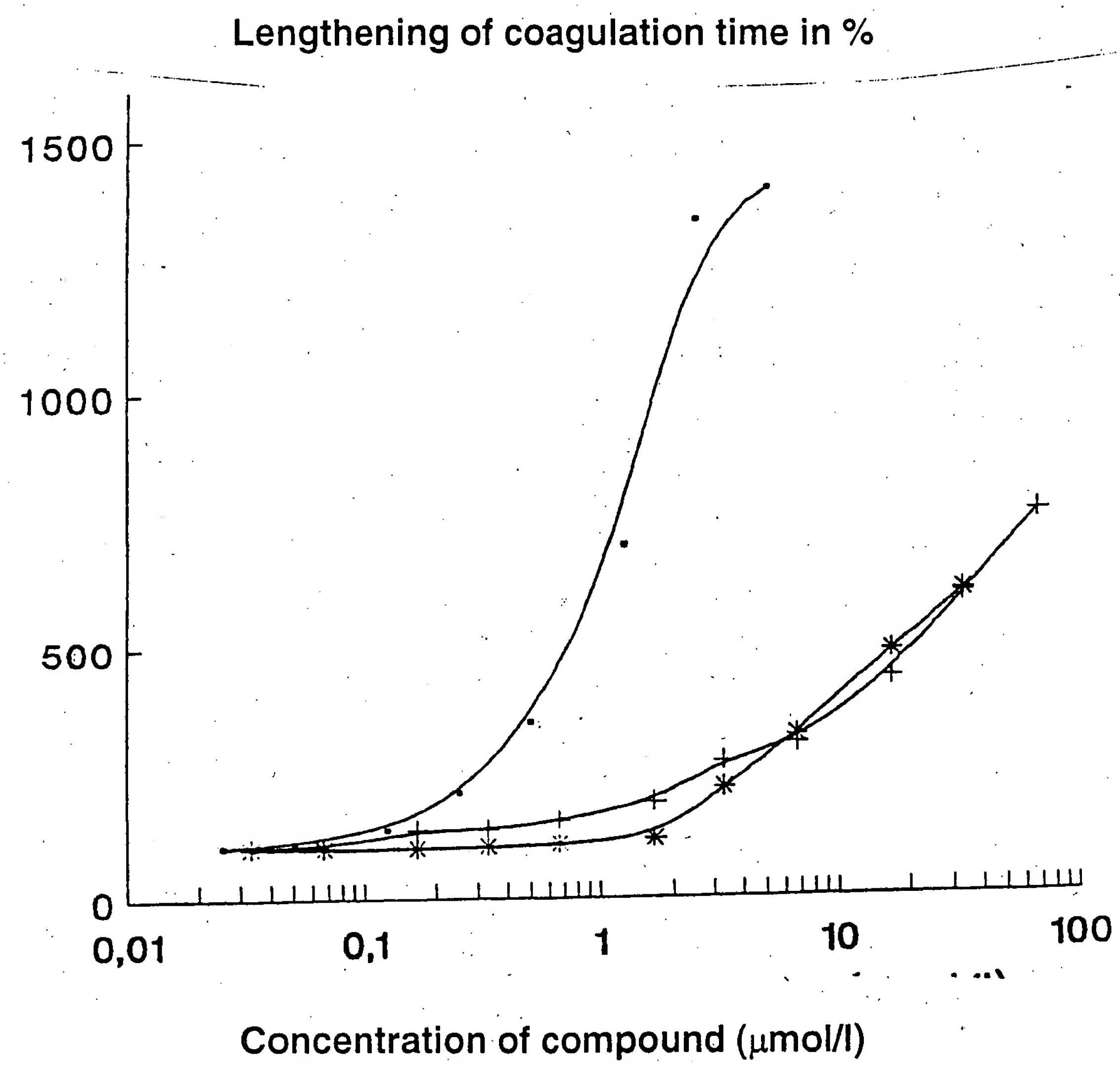
4. Orally, anally, subcutaneously or intravenously administrable, antithrombotically active pharmaceutical preparation , characterized by an effective amount of at least one phenylalanine derivate in accordance with patent claim 1 or 2 and suitable pharmaceutical adjuvant substances.

5. Antithrombotically effective pharmaceutical preparation in accordance with patent claim 4 in the form of tablets, dragées, capsules, pellets, suppositories, solutions or transdermal systems, like patches.

6. Method for coagulation or, respectively, thrombin inhibition in living creatures, in particular in humans, through administration of an effective amount of at least one compound in accordance with either patent claim 1 or 2 or, respectively, a pharmaceutical preparation in accordance with one of patent claim 4 or 5.

Illustration 1

Lengthening of Coagulation Times by Compound 57 <u>in vitro</u>

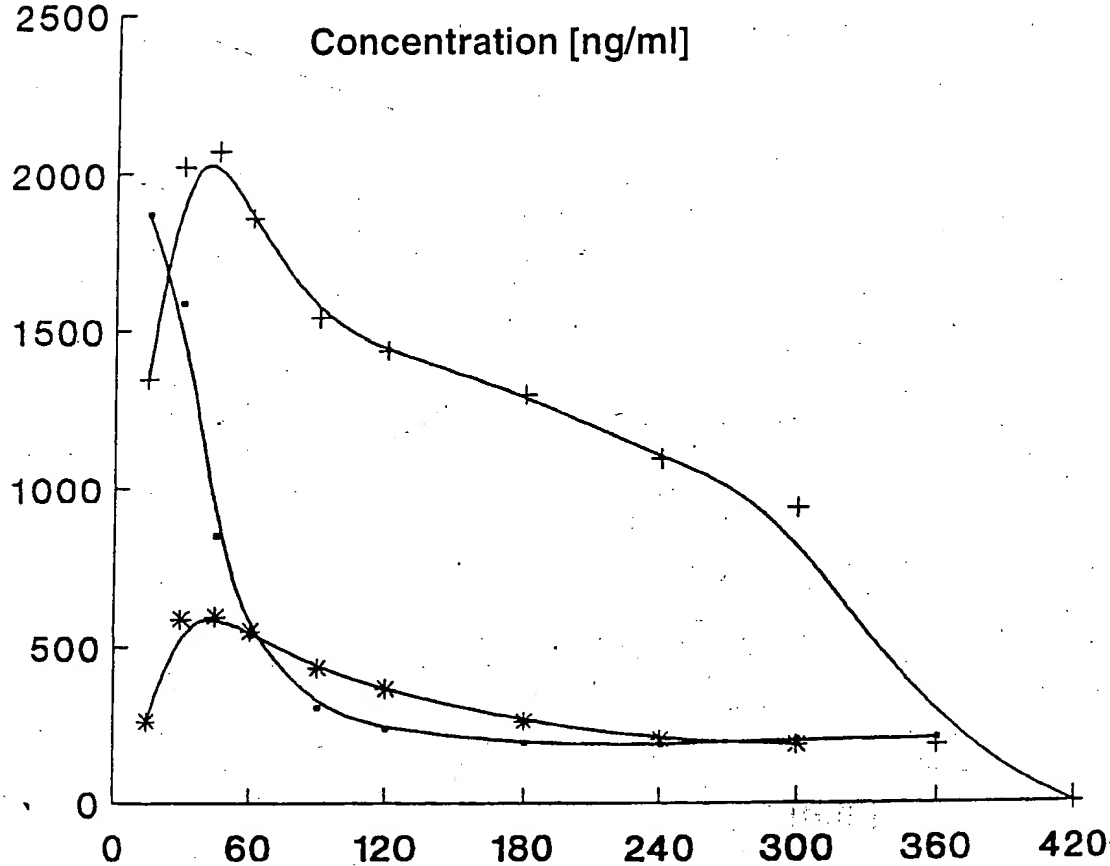


Thrombin time

a PTT

Prothrombin time

Illustration 2: Plasma levels of compound 26 after p.o. + s.c. application and compound 36 following s.c. application



100 mg/kg p.o.

5 mg/kg s.c.

Cpd. 36 (s.c.)

eof